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GROWTH AND DEVELOPMENT OF FUNCTION IN BLOOD VESSELS AND LYMPHATICS *

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PROBLEMS relating to the growth and development of function in blood vessels and lymphatics are not restricted to the period of embryonic development and the growth period, but are met with throughout the entire life of the individual. They play a particularly important rôle in the reparative stages of inflammation, in the reaction to various forms of injury, and in the healing which follows surgical operations. The development in our laboratory of a special technic enables us to make observations of many continuous hours daily, extending over weeks and months, with the highest powers of the microscope, in which we can observe directly the minutest morphological details of the growth of blood capillaries, the differentiation of arteries and venules and their behavior in relation to function, and the growth and behavior of lymphatic vessels.

The method, first worked out with the assistance of Mr. Sandison and perfected and extended by a group including Drs. R. G. Williams, H. T. Kirby-Smith, R. O. Rex, R. G. Abell, W. J. Hitschler, Mrs. Clark and myself, consists of the permanent installation in the ear of a rabbit or other mammal of a double-walled transparent chamber, in which there is left a central round " table " space, in relation with the living tissue of the ear. This space fills with exudate, blood cells and fibrin, which in turn is invaded by new tissues—including blood-vessels, lymphatics, connective tissue, and nerves—from the surrounding living tissues. The thickness of the space varies in different chambers from 45 to 75 micra. Modified types of chamber are also in use which permit the study of the original tissues of the ear, the introduction of chemical substances (Abell and Clark), and the access to the living tissue for experiment, transplantation or manipulation (R. G. Williams). No anesthesia is required during the observation period.

First the rate of growth of new blood capillaries will be considered. They appear at the edge of the " table " at an average of seven days after the installation of the chamber and advance at a rate which varies from 0.2

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to 0.6 mm. a day, under favorable growth conditions. There is evidence that the rate of advance may be influenced by temperature, at least to the extent that marked lowering of the room temperature may result in slower growth. There is also evidence that the rate of advance is affected by the condition of the substances into which the capillaries are growing. Thus in chambers with a minimum of disturbance, in places where no hemorrhages or inflammatory exudations have occurred for several days, the rate of growth is appreciably reduced. However, there is much still to be learned regarding the physical and chemical factors which regulate the growth of new capillaries, and studies in this direction are going on in our laboratory.

Regarding the manner of growth of new blood capillaries, it has been possible to establish definitely that they grow by the sending out of sprouts from preëxisting capillaries, in a manner similar to that established years ago in the transparent tails of amphibian larvae. Pointed endothelial processes are pushed out from the side of a circulating capillary or venule into the base of which the lumen gradually extends, and into which the nuclei are carried by the ameboid activity of their surrounding endoplasm. The tip is constantly extended until it comes in contact with a blood capillary, venule or another sprout, when it forms a connection through which the lumen gradually extends. The nuclei increase in number by mitotic division —a process which has been observed in the living rabbit. No outside cell contributes to this endothelial extension. In fact, such sprouts have been seen to grow through a fibrin network—which no fibroblasts had yet penetrated and in which leukocytes could be easily excluded as possible contributors. The number of new sprouts for a given area varies enormously —from an occasional single sprout to a density so great that the neighboring sprouts are almost in contact with one another. Many sprouts may grow out from the wall of a single capillary or venule. Since this property of growth is probably common to endothelium of all capillaries and veins, it may be stated that, if suitable growth conditions are introduced, the number of capillaries of any region of the body may be increased many-fold within a period of two or three days.

However, growth processes also operate in the reverse direction, and many of the newly formed capillaries retract or disappear, in some instances by a process which is the reverse of sprouting, in others by what appears to be a dissolution of the endothelium. Thus, in places not more than one out of 10 of the newly formed capillaries survives, while in others nearly all may survive. Loss of capillaries is greater in the neighborhood of arterioles than in that of venules. This process of reverse growth, while varying in rate, may occur so rapidly that short capillaries may narrow and retract within 24 hours.

Nearly as rapid as the growth of new capillaries is the development of arteries and veins, both of which are formed by the enlargement of capillaries or parts of capillaries. Within a few days a newly formed capillary

may enlarge to form part of an arteriole or venule. The determining factors as to which of four fates may befall a capillary (retention as a capillary, disappearance, or enlargement to form part of an artery or vein) lie chiefly in the two hydrodynamical forces, blood pressure and amount of blood flow, as pointed out by Thoma in his histomechanical principles, the former regulating the thickness of the wall and the latter the size of the lumen.

While the endothelium is the essential tissue of the vascular system, forming a complete lining probably for all parts of it, leading the way in all its growth extensions and constituting a membrane through which occurs all interchange between the blood stream and outside cells and spaces, there is an elaborate development of accessory or adventitial cells outside, which ranges from the smooth muscle, connective tissue, elastic tissue wall of the larger arteries to scattered adventitial cells on capillaries and venules. These layers act as mechanical supports to the system and also, in connection with the nervous system, as local regulators of the flow of blood. Regarding these tissues outside the endothelium we have been able to make certain interesting observations.

The first adventitial cells on blood capillaries appear very early in their formation, often on new sprouts which have not yet connected with other capillaries and practically in all cases soon after circulation starts in the new capillary. In the tadpole's tail their formation from the surrounding connective tissue cells has been established by Mrs. Clark and myself, and we have observed in the mammal the flattening on the newly forming capillary of cells from outside—from the army of fibroblasts which usually invades the space along with the blood capillaries. Persistent study of some 40 such cells carried out during the past three weeks on a set of about a dozen capillaries indicates that the original early quota may remain unchanged for weeks, although one cell was seen to undergo division into two. In the capillaries in the rabbit's ear they are as inert as we had found them in the tail of the tadpole, and we cannot agree with Krogh, who has rather unfortunately termed them " Rouget " cells, that they play any part in capillary contraction.

On the arterioles there is a rapid increase in the number of cells outside the endothelium, the exact origin and development of which have not yet been worked out. However, the tempo and certain other details of development are of interest. Within two or three days one sees on the arterioles, in place of the longitudinally arranged cells, a continuous layer of cells which encircle the arteriole. Coincident with or following soon after this the arteriole becomes narrower. Just how soon this cell may be called a muscle cell we do not know. It apparently does not perform definite contractions and dilatations unless and until a vasomotor nerve reaches it. Regarding the latter, Dr. R. G. Williams, Mrs. Clark and I have been able to link up the inauguration and extension of definite contractions and dilatations with the ingrowth of nerves, by the use of intravital methylene blue

staining, and have proved the presence of active muscle cells which performed nerve controlled contractions on a vessel which 10 days before had been a newly formed capillary sprout. We also observed the extension of this undoubted contractility to muscle cells on parts of the vessel which ranged between 10 and 18 days of age. We have evidence of definite muscle contractility on arterioles 8 and 9 days old, respectively, which must for the present stand as the minimum time in which a new smooth muscle cell may develop. While muscle cells develop on all arterioles and apparently maintain a persistent partial contraction, only a variable fraction of the new arterioles in a regenerated region are reached by vasomotor nerves, and it is only the latter which develop typical contractions and dilatations. Thus we have some chambers in which not a single arteriole showed this activity even after months. However, we have seen active contractility develop as late as 7½ months after the growth of the arteriole.

While capillaries ordinarily intervene between artery and vein, it has long been known that in the ears of rabbits, as in certain regions of other animals, there are direct connections, or arterio-venous anastomoses. It has been possible in our chambers to observe the behavior of such structures, to watch their development and to discover some of the factors which regulate their formation and persistence. They are regulated in part, at least, by circulatory conditions.

In speaking of the development of the arteriole we have referred also to its function. Let us return briefly to consider the development of function in the capillary. We may exclude the development of contractility in the capillary, since the most prolonged observation and rigid testing, first by Sandison and later by Mrs. Clark and myself, have convinced us that neither in the ear of the rabbit nor in that of the dog does endothelium possess any such power of contractility as is usually associated with control of blood flow. This is of extreme interest and importance; of interest because the endothelium of capillaries in the tail of amphibian larvae has undoubted active contractility (and suggests an evolutionary loss of this property following the elaborate development of the nerve-muscle apparatus on the arteries in mammals); and of importance because it directs the physiologist back to smooth muscle and nerve in analyzing the control of peripheral circulation, perhaps saving him from a wild-goose chase in an attempt to discover the details of an endothelial contractility which probably does not exist in the mammal.

Regarding the essential function of the capillary, however, that of furnishing a membrane through which interchange of substances takes place, it is interesting that this function apparently starts as soon as circulation begins in a new capillary—perhaps earlier. However, the newly formed capillary differs slightly from the older capillary in its consistency, for it is obviously softer and more tender. Thus newly formed capillaries frequently become widened to a diameter three or four times the usual capillary size and are so tender that small hemorrhages from them are easily produced

by slight external pressure or even by increased blood pressure. This soft consistency changes rapidly, especially in those capillaries with abundant blood flow, and within a day or two the new capillary grows narrower and is more resistant to injury.

The soft consistency of the young capillary is a property which may be manifested by well-established capillaries under the influence of chemical substances. There is evidence that blood-vessel endothelium may at any time, in reaction to certain chemical or mechanical stimuli, undergo progressive changes in consistency which are evidenced by (1) mild sticking of leukocytes to the endothelium, (2) prolonged leukocyte sticking, (3) emigration of leukocytes, (4) localized bulgings and hemorrhages, and (5) disintegration of endothelium. Such changes are most conspicuous in but not confined to inflammation.

The growth of lymphatics as observed in the rabbit's ear shows both similarities and differences when compared with blood vessels. Like blood vessels, growth takes place by the sending out of endothelial sprouts, into the bases of which the lumen gradually extends. All new lymphatic endothelium forms from preëxisting lymphatic endothelium, and nuclei increase in number by mitotic division. The lymphatic is *normally* closed, both during growth and subsequently.

On the other hand, the growth of lymphatics is much more sporadic than that of blood vessels. Thus in the many chambers which have been observed, there have been great variations in the time and extent of ingrowth of lymphatics. In some cases one or more lymphatics have grown along with the most advanced blood capillaries, in others the first lymphatics have not appeared on the table until a week or more after the space has been completely vascularized. When lymphatics advance after blood vessels and connective tissue have differentiated, they show a decided tendency to grow along a clear space next an artery or a vein. They may continue a slow growth for weeks. Because of the almost negligible pressure in lymphatic capillaries they may be compressed along their course, and terminal stretches may be left completely isolated. Such isolated lymphatics may persist for weeks, retaining their typical lymphatic endothelial properties. They may eventually reunite with other lymphatics or may gradually shorten and disintegrate.

While lymphatics are normally closed, their contents may be forced through the wall by light pressure. If surrounded by the normal semigelatinous intervascular material, openings so made close at once. If, however, there is free fluid surrounding them, we have observed such artificial openings to persist for days, with an in-and-out movement of fluid and floating cells.

The frequent close proximity of venule and lymphatic makes possible a break of the double endothelial wall, with hemorrhage into the lymphatic. Such openings have, in our observations, always closed immediately, leaving a mass of blood in the lymphatic. While such a mass of erythrocytes in

the lymphatic may be cleared out within 24 hours, some of the erythrocytes may, in the absence of massage, remain in the bulbous tips for many days.

As for the development of function in the lymphatic, we have been impressed with the very slight amount of activity manifested by the lymphatic capillaries as watched in the living, under the conditions of our observations. There is some passage of fluid into the new vessels, but it is apparently slight in amount. Thus floating cells in the lymph may be seen bobbing back and forth for minutes or even hours without progressing. We have frequently seen not only erythrocytes but immigrated leukocytes remain in a lymphatic tip for weeks. The lymphatics play no significant part in the removal of the enormous amount of extravasated erythrocytes and other débris which is present following the insertion of the chamber or after a hemorrhage, and which is removed without their assistance. In inflammatory conditions with edema the lymphatics become distended but usually show even a diminution in flow indicating a blocking. There is no noticeable difference in the rate or amount of connective tissue growth in our chambers, whether lymphatics are present or absent. Regions without lymphatics show no evidence of disturbed physiology. In short, our own observations on the behavior of living lymphatics corroborate other studies on the sluggishness of lymph flow from peripheral parts of the body in mammals, in the absence of muscular activity. They even raise the question as to whether, in such regions, lymphatics play any useful rôle whatever.

The observations which have been presented in this paper regarding the growth and behavior of blood vessels and lymphatics as seen through the microscope in the living mammal represent but samples of the studies which a new method has made possible. They form a mere beginning of a new analysis of that region which is of such fundamental importance in the anatomy and physiology of health and disease; namely, the peripheral region which includes the arteriole and venule, the blood and lymphatic capillary, the cells of the tissues, and, scarcely less important, the extravascular, extracellular tissue spaces.

The paper was illustrated by lantern slides and by an eight minute motion picture film made with the assistance of Dr. E. A. Swenson, which showed the circulation in new-growing and recently formed blood vessels, movement of blood cells in an isolated lymphatic, and contraction and dilatations of a new-formed arteriole and of a new-formed arterio-venous anastomosis.

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THE PRESENT STATUS OF BRONCHOSCOPY IN BRONCHIAL ASTHMA*

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In a discussion of bronchial asthma one should bear in mind that patients sent as cases of asthma for investigation or treatment often present signs or symptoms that do not conform to the textbook description of this condition. In other words, there are many pathologic conditions that simulate asthma and may be regarded clinically as such. It is only by a careful study that the correct diagnosis is made. The rôle of bronchoscopy in bronchial asthma therefore includes the investigation of the tracheobronchial tree to rule out certain conditions that might simulate asthma. In addition bronchoscopy permits the collection of bronchial secretions for autogenous vaccine, and it affords relief by removal of obstructing secretions from the air passages. The interest of the bronchoscopist is limited largely to that form of asthma associated with evidences of tracheobronchitis, the so-called bacterial asthma. Hypersensitiveness and the part played by bacteria as an etiological factor in asthma are problems for the allergist.

The matter of diagnosis is often difficult. Not infrequently patients with dyspnea, wheeze or cough of obscure origin are referred to the bronchoscopist for investigation and it is found these are clinical manifestations of hypersensitiveness. On the other hand patients with a foreign body in the air passages or even in the esophagus not infrequently have been studied carefully from an allergic standpoint, and only later has it been discovered that there was a good foreign body history with quite typical signs and symptoms.

One of the common and often most misleading symptoms which suggest a provisional diagnosis of asthma is wheezing respiration. It is usually described as " asthmatoid wheeze," a term which promptly offers a diagnostic possibility to those who are readily influenced by suggestion. The wheeze, heard best at the open mouth and towards the end of expiration, should be considered as an audible manifestation of *narrowing of the airway*. Mechanical conditions producing the wheezing sound are perfectly obvious to the bronchoscopist; namely, air being forced through a narrowed lumen. In the patient with foreign body the narrowing is produced by the foreign body, swollen inflammatory mucosa and secretions; in the asthmatic patient air is being forced through a lumen narrowed by congestive or inflammatory changes, and with thick mucoid secretion adherent to its walls. It has been described also as a symptom of laryngeal disease, of foreign body in the trachea or bronchi, of foreign body in the esophagus, of malignant or benign tumor of the treachea or bronchi, of compression stenosis or of stricture of a bronchus. Why not describe it as " wheeze " or " wheezing

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respiration" without reference to asthma and then proceed to investigate it as a symptom indicative of partial obstruction to the airway? It is in this connection that bronchoscopy and at times esophagoscopy have given valuable aid in establishing a correct diagnosis and often effecting a cure. Illustrative cases are cited:

Case 1. A woman, aged 31 years, reported to an Allergy Clinic for investigation of wheezing respiration and a slight cough of three weeks' duration. Routine skin tests were carried out, and the patient was requested to bring in a quantity of house dust. Following the third visit she was advised that all of the tests were negative and that she did not have asthma. Curiously, the wheeze disappeared at about that time, being replaced by slight dyspnea and an aching sensation in the left chest. She consulted another physician who examined her chest and referred her to the Bronchoscopic Clinic of Jefferson Hospital for investigation of atelectasis of the left lung. Completed studies revealed a malignant tumor of the left bronchus.

Comment. The symptom "wheezing respiration" led the patient to believe that she had asthma. This provisional diagnosis apparently was accepted at the Allergy Clinic, for no chest studies were carried out. When the bronchial obstruction became complete, producing atelectasis, the wheeze disappeared.

Case 2. A child, aged two years, began to wheeze during August. This was noted particularly during sleep. There was also some dysphagia for solid food. Later, slight dyspnea developed. After several months it was observed that paroxysms of dyspnea with wheezing occurred whenever the child took any food. A diagnosis of asthma was made and several foods were suspected. Avoidance of these gave no relief. The symptoms became progressively worse; epinephrine afforded some comfort. On careful questioning it was found that the child had swallowed a large button about three weeks before the onset of symptoms. Roentgen studies of the swallowing function revealed a non-opaque object in the cervical esophagus. At esophagoscopy this proved to be a button. Its removal seven months after it had been swallowed was followed by prompt relief of the asthmatic symptoms.

Comment. The large size of the foreign body together with the periesophageal swelling produced compression stenosis of the trachea which was responsible for the wheeze and later the dyspnea. The dysphagia apparently was overlooked.

Foreign body as a diagnostic possibility should be excluded in every child presenting symptoms suggesting asthma. A careful study of the history and symptoms, a thorough physical examination of the chest supplemented by a roentgen study will rule out foreign body in a majority of cases. If in doubt a diagnostic bronchoscopy is indicated. Wheezing respiration is a common symptom of bronchial foreign body.

Bronchoscopic observations in the cases of true asthma are of interest. The noteworthy findings are collapse of the trachea and bronchi during cough and forced expiration, and the presence of abnormal secretions.

Collapse of the Trachea and Bronchi. Moderate forward bulging of the membranous wall of the trachea during cough is often observed in children, occasionally in adults, and is not considered pathologic. In the normal person there is a rhythmic movement of the trachea and bronchi during respiration. The bronchi elongate and dilate during inspiration; during expiration they shorten and contract. These changes are participated in by the entire bronchial tree. The collapse observed in certain cases of asthma differs from the normal phenomenon both in appearance and in the mechanism involved in its production. At the beginning of expiration in many cases there is noted marked collapse of the trachea. In some the collapse is limited to the posterior tracheal wall, which, bulging forward, becomes convex, and fits into the concavity of the anterior wall of the trachea; the resulting lumen is crescentic. The forward bulging occurs during expiration and cough, and is in proportion to the force of the expiratory effort. Occasionally the lateral tracheal walls also participate in the collapse, giving the lumen a triangular appearance. The lumen promptly returns to its normal more or less rounded appearance at the beginning of inspiration. In many of these cases there is an associated collapse of the walls of the bronchi including the orifices of the bronchial subdivisions. These changes often are sufficiently marked to interfere with the introduction of the bronchoscope which can be advanced only during inspiration. This is not bronchial spasm. The collapse is undoubtedly passive in nature, and one gains the impression that the tracheal and bronchial walls are being forced shut by some external influence. This phenomenon was discussed by F. J. Kalteyer in a previous report. While not absolutely characteristic of the average case of asthma, it is unquestionably a pathologic state that is present in certain of the different conditions clinically described as asthma.

Treatment. In my experience bronchoscopy has been employed only in cases that did not present any demonstrable etiological basis for their symptoms or did not respond to treatment based on supposed causative factors. With an occasional exception our patients had been studied from the standpoint of allergy; and the nasal accessory sinuses, the teeth and other possible foci of infection had been investigated. Their status as to the presence or absence of serious organic disease had been determined.

These patients could be divided roughly into two groups. The first consisted of adult patients who, previously well, dated the onset of asthmatic symptoms to an acute respiratory infection. The second group consisted largely of children. In these the asthmatic symptoms were sudden in onset and often were considered as of foreign body origin.

In the first group the more commonly observed symptoms were a sense of tightness or constriction about the chest and cough. Paroxysmal attacks of coughing often initiated the asthmatic attacks. Mucoid or thick mucopurulent sputum was present. When sputum was readily coughed up the patient seemed comfortable. From a description of the paroxysms of asthma one gained the impression that the inability of the patient to get rid

of secretions was followed by subjective sensations in the chest, paroxysms of cough with dyspnea and wheezing. The hypodermatic use of epinephrine often gave little relief; occasionally it produced a feeling of depression with severe headache. Atropine and morphine often were helpful. Burning of "asthma powders" seemed to give greater temporary relief than any of the commonly employed measures. Attacks would continue for hours, even days. Relief was secured following expectoration of secretions. The patients commonly exhibited the clinical and roentgen findings observed in chronic laryngotracheobronchitis. Suppuration of the nasal accessory sinuses often was present but no relief was secured from treatment. A history of many nasal operations was the rule. It was not uncommon to find allergic reactions to certain substances including house dust. Attempts at desensitization either failed to give relief or produced only slight amelioration of the attacks.

The bronchoscopic findings consisted of moderate inflammatory changes involving the mucosa of the larynx, trachea and larger bronchi with thick mucoid or mucopurulent secretion adherent in small clumps to the walls. One always could secure an additional quantity of this by exploring the smaller bronchial subdivisions with a small flexible tipped aspirating tube. Narrowing of the orifices of the smaller bronchial subdivisions was no greater than would be expected in the presence of chronic inflammatory swelling of the mucous membrane. Collapse of the trachea and larger bronchi during expiration occurred. Patients observed during a paroxysm did not yield any additional information unless dyspnea was marked. Then the expiratory collapse of the airway was increased and the mucosa appeared more cyanotic.

The following fairly typical case is cited:

Case 3. A female, aged 25 years, had asthmatic attacks for six years. There was a history of an acute pulmonary infection about two years previously, but recovery was apparently complete. Shortly before the onset of the asthmatic attacks the patient had a severe "head cold" which continued for about two months. During the past six years she had been under the care of many physicians; 10 operations on the nasal accessory sinuses had been performed, and in addition the tonsils had been removed. A number of skin tests were carried out with negative results and vaccine therapy was employed with little benefit. During the year prior to admission to the Bronchoscopic Clinic, Jefferson Hospital, she had secured little relief from attacks. On admission she had not been free from wheezing and dyspnea for practically three months. The usual forms of medication gave slight relief. A roentgen study of the chest revealed little change. Although the patient's condition was not good bronchoscopy was proceeded with. A large quantity of thick tenacious mucopus was found in the trachea, main bronchi and their subdivisions. There was a generalized tracheobronchitis. Collapse of the trachea and large bronchi was noted during expiration and cough. The patient developed a severe paroxysm of asthma during the bronchoscopy; with removal of a large quantity of secretions there was marked alleviation of symptoms. Vaccine made from the bronchoscopically removed secretions was given with no apparent benefit. Repeated bronchoscopic treatments have been carried out in this patient, in fact, she has been reporting to the Bronchoscopic Clinic

every three or four weeks for the past four years. She is willing to continue since this is the only mode of treatment that has afforded relief.

The second group of cases was characterized by the abrupt onset of the asthmatic symptoms, often suggesting foreign body aspiration. All of the patients observed were children. In one case the attacks occurred only during rainy weather. In others no predisposing factors could be elicited. The acute onset with wheezing respiration, alarming dyspnea both expiratory and inspiratory, a moderate febrile reaction and clinical and roentgen findings of bilateral obstructive emphysema warranted bronchoscopic investigation to rule out tracheal or bilateral bronchial obstruction, notably foreign body. Through the bronchoscope there was found a subacute tracheobronchitis with a large quantity of tenacious, greyish secretion in the trachea and bronchi. The relief secured following bronchoscopic aspiration of the secretions was not unlike that observed after removal of a partially obstructing tracheal foreign body. In the subsequent studies of these cases nasal accessory sinus disease and positive skin reactions, particularly to foods, often were found present. I do not recall a single case in this group, however, that was benefited by removal of suspected foods or by attempts at desensitization.

The following case is typical:

Case 4. A child, aged two years and nine months, daughter of a physician, was brought to the Bronchoscopic Clinic with wheezing respiration and severe dyspnea. There was moderate fever. The onset had occurred quite abruptly 24 hours previously. A provisional diagnosis of asthma had been made, and epinephrine, atropine and morphine had been given without relief. Foreign body was then suspected although there was no history of foreign body aspiration. On admission the dyspnea and wheezing were both expiratory and inspiratory. There was no cyanosis. Cough was absent. The findings suggested tracheal obstruction. Roentgen study by Dr. W. F. Manges showed overdistention of both lungs with air throughout the entire respiratory cycle suggesting either a foreign body in the trachea or any condition that would produce partial obstruction to both main bronchi.

At bronchoscopy a large quantity of thick mucoid secretion was removed from the trachea and both main bronchi. There was no evidence of aspirated foreign body. A roentgen study made following bronchoscopy indicated that there was a marked decrease in the degree of overdistention of the lungs. Wheezing and dyspnea were absent. There was roentgen evidence of nasal accessory sinus disease. Skin tests were carried out and were found positive for two foods, namely chicken and beef. Their use, however, did not produce symptoms. On close questioning it was learned that this patient had slight dyspnea lasting for about one hour three weeks previously. Treatment of the sinuses has since been carried out and the patient has had only occasional slight attacks of wheezing.

It is believed that in both of these groups, one occurring in adults, the other in children, there was an intrinsic cause for the asthmatic attacks. Sinus disease was present in a majority of cases.

In the first group there was found evidence of a chronic infection of the

mucosa of the tracheobronchial tree. Treatment of the sinus infection when present and attempts at desensitization gave slight relief and to only a few cases. Bronchoscopy with removal of secretions gave prompt relief. When bronchoscopy was repeated at intervals the attacks either did not recur or produced only slight distress.

In the second group the findings suggested an acute inflammatory process. Bronchoscopic aspirations afforded prompt temporary relief. Treatment of a sinus infection when present gave the best ultimate results.

It is difficult to state how bronchoscopy is helpful in these cases unless it is the result of removal from the bronchi of thick secretions that interfere mechanically with the exit of air during expiration. There can be no question that bronchoscopy is of value. If the symptoms are the result of simple mechanical obstruction of bronchi one would expect patients with extensive bronchiectasis to exhibit symptoms of bronchial asthma. The occurrence of obstructive emphysema and particularly a patchy obstructive atelectasis undoubtedly exerts an influence although this is difficult to prove. Lobar atelectasis as a complication of asthma has been described by Clarke and others. It was my privilege to observe Clarke's case bronchoscopically. The bronchoscopic observations made did not permit one to arrive at definite conclusions.

The coexistence of asthma with bronchiectasis is not frequent, although I believe that it is more common than medical literature indicates. It is probable that the asthma antedates the bronchiectasis. In spite of this, however, the asthmatic attacks are more frequent and severe when the bronchiectasis does not drain properly. The presence of bronchiectasis can be positively determined only by the introduction into the bronchial tree of iodized oil. Although this has been done in a number of cases without untoward results one death did follow its use. This patient, a woman, had frequent paroxysms of severe asthma for many years. There was evidence of bronchopulmonary disease. During the bronchoscopic aspiration of secretion she developed a paroxysm of asthma; about 9 c.c. of iodized oil were instilled into each of the lower lobe bronchi. Dyspnea increased and death ensued within 20 minutes. The cause could not be determined. No autopsy was permitted and it was not learned if bronchiectasis was present. Since bronchoscopy affords the best opportunity for the collection of material for the preparation of autogenous vaccines a word of comment on the use of such vaccines may be added at this point. The empiric use of autogenous vaccines in asthma may not be considered wholly scientific when there is doubt concerning the exciting factors. In spite of this, however, satisfactory results have been secured from such vaccines in a sufficiently large percentage of obscure cases of asthma to warrant their employment. In a previous communication I reported a case of asthma that secured complete relief of symptoms from the use of vaccine made from bronchoscopically removed secretions. This patient had been treated by several competent allergists without benefit. Two additional cases have now se-

cured complete relief following the use of autogenous vaccines. I believe therefore that they should be employed in selected cases.

Summary

Bronchoscopy is of value in the study of certain clinical conditions described as bronchial asthma. No allergy or asthma clinic is complete without the services of a competent bronchoscopist.

Bronchoscopy should be given a trial in the treatment of cases of bronchial asthma that do not respond to commonly employed methods. The best results are secured in cases with tracheobronchitis, excessive secretions or bronchial obstruction.

Vaccines made from bronchoscopically removed secretions are of value in cases of so-called bacterial allergy.

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PROGNOSIS IN ACUTE GLOMERULAR NEPHRITIS*

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THE outlook for adults who have acute glomerular nephritis has seldom been the subject of comment in the literature. Excepting war nephritis, the few studies on prognosis are mostly in children. The mortality during the acute stage of the disease is regarded as low in both groups; but both the immediate and the late prognosis are apparently more favorable in the earlier ages. However, the death rate during the acute stage in the cases of acute nephritis, chiefly adults, recently reported by Murphy, Grill and Moxon,[1] was so high as to challenge the truth of these beliefs.

The present study was undertaken to determine what had been the experience at the Peter Bent Brigham Hospital in this regard. One hundred cases of typical, acute, diffuse glomerular nephritis were selected from 160 so diagnosed during the years 1913 to 1934, and the ultimate outcome determined by a follow-up study which was successful in disclosing the renal condition of all but 13 of the 90 individuals who survived their acute illness. The data are extraordinarily complete because of the constant interest in the disease shown by Dr. J. P. O'Hare and Dr. Henry A. Christian. Sixty cases were rejected because of one or more features which suggested that they were probably instances of chronic nephritis with acute exacerbation. All but one of the cases were observed in the hospital for an average of six weeks during their acute process; and the one exception was treated at home by Dr. O'Hare. It was, therefore, possible to observe almost all of the patients throughout the early stages of their disease.

Acute Stage. As can be seen in table 1, there were twice as many males as females. The age incidence varied from 12 to 59 years, the former being the lowest age limit for admission to the medical service of this hospital.

Acute nephritis is most common in children and young adults. This is the period of life when the causative acute infections of the upper respiratory tract are most frequent. Three-fourths of this series were between 12 and 30 years; only seven were above 40 years.

Ten patients died during the acute stage. In five, death was not attributed to the nephritis but to the causative infection, or to an incidental factor such as acute syphilitic meningitis, broncho-pneumonia, lobar pneumonia, hemorrhage from carcinoma of the cecum, and generalized peritonitis from perforation of a typhoid ulcer. Of the five patients whose death was due primarily to acute nephritis, four were in the third decade and one in the sixth. Three died of uremia, one of broncho-pneumonia and severe fatty degeneration of the liver, and one of erysipelas. The complicating

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TABLE I

Age and Sex Incidence in 100 Cases of Acute Nephritis with Outcome in Relation to Age

Age, Years	Number of Cases	Females	Males	Died of Acute Nephritis	Died of Etiologic Disease or of Incidental Cause	Became Chronic	Cured	Renal Condition Unknown
12–20	39	14	25	0	1	5	28	5
21–30	35	12	23	4	2	7	18	4
31–40	19	6	13	0	0	3	12	4
41–50	4	1	3	0	0	0	4	0
51–60	3	0	3	1	2	0	0	0
Total	100	32	68	5	5	15	62	13

diseases in the last two cases developed about two weeks after the onset of acute nephritis.

The etiologic factors, as can be seen in table 2, are similar to those given by others.[2, 33] Infections of the upper respiratory tract, including tonsillitis, pharyngitis, peritonsillar abscess, the common cold, and otitis media, accounted for 66 per cent; while in 15 cases, an etiologic factor could not be

TABLE II

Etiology of 100 Cases of Acute Nephritis with Relation to Outcome

Etiology	No. of Cases	Died of Acute Nephritis	Died of Etiologic Disease or of Incidental Cause	Cured Cases	Became Chronic	Renal Condition Unknown
Sore throat; tonsillitis	28	1	2	20	3	2
Common cold; grippe. (Associated with sinusitis, pleurisy, cervical adenitis, or rheumatic fever—4 cases)	27	1	1	18	4	3
Peritonsillar abscess	9	2	0	3	1	3
Pneumonia (lobar—4 cases)	5	0	1	2	2	0
Scarlet fever	4	0	0	3	0	1
Cold (exposure)	3	1	0	2	0	0
Typhoid fever	2	0	1	1	0	0
Otitis media	2	0	0	2	0	0
Erysipelas	1	0	0	1	0	0
Mumps	1	0	0	1	0	0
Purpura	1	0	0	0	1	0
Rheumatic fever	1	0	0	1	0	0
Influenza and empyema	1	0	0	0	0	1
Unknown	15	0	0	8	4	3
Total	100	5	5	62	15	13

determined. The onset of acute nephritis followed scarlet fever in only four patients. The infrequency of postscarlatinal nephritis in this series is probably due to the fact that cases of scarlet fever are rarely admitted to this hospital. Three of the four cases of postscarlatinal nephritis occurred in brothers at about the same time, and could be classified as cases of so-called familial nephritis.[3] These three are now cured, 16 years later. The remaining case did not return for follow-up study. Lobar pneumonia (in four cases), and broncho-pneumonia (in one) accounted for 5 per cent of the cases of acute nephritis. Rheumatic fever is rarely the cause of true glomerular nephritis,[4] but it is the attributed cause in one of our cases. Another patient, following his second attack of rheumatic fever accompanied by an acute upper respiratory tract infection, developed acute nephritis which was believed due to the latter infection. The urine of this patient had not cleared at the end of three weeks, and he died of influenza a few months later. Mumps is not usually considered a cause of acute nephritis; however, one patient, aged 20, following an attack of epidemic parotitis, developed typical acute glomerular nephritis. Although the urine had not cleared during four months of observation, 14 years later there was no evidence of chronic nephritis.

Table 3 shows the frequency of the various symptoms and signs. Significant early symptoms and signs of acute nephritis may be absent, the

TABLE III

Symptoms and Signs in 100 Cases of Acute Nephritis

Symptoms and Signs	Per cent	Symptoms and Signs	Per cent
Albuminuria	100	Diarrhea	3
Microscopic hematuria	87	Constipation	3
Edema	65	Anuria	3
Gross hematuria	42	Dyspnea	3
Headache	18	Coma	3
Nausea and vomiting	15	Pain in epigastrium	3
Oliguria	11	Transient blindness	2
Backache	10	Mental confusion	2
Convulsions	9	Dizziness	1
Frequency of urination	6	Pains in joints	2
Fatigue	6	Purpura	1
Dysuria	3	Congestive heart failure	1

diagnosis being incidental to a routine urine examination. This was true in 14 of our cases. Edema, non-uremic convulsions, hypertension, neuroretinopathies, myocardial failure, uremia, gross hematuria, and albuminuria were the only signs which seemed possibly related to the outcome of the nephritis.

Edema which occurred in two-thirds of both the cured and the chronic cases was usually confined to puffiness about the eyes and swelling of the ankles. There was no relationship between the degree or duration of edema and prognosis. As is usually true in acute nephritis, the amount of total protein, albumin and globulin of the blood was normal, or but slightly lowered, in the few cases in which these determinations were made.

Hypertensive encephalopathy manifested as convulsive seizures is not uncommon in acute nephritis, especially in children. Of the 100 cases, nine between the ages of 12 and 37 years had convulsions. All of them had hypertension and a normal or only slightly elevated blood urea nitrogen. In seven, the convulsions were due to hypertensive encephalopathy, while there was probably another cause in the other two. One of these died of acute syphilitic meningitis about two weeks after the onset of acute nephritis. The other patient is most interesting. The convulsions, first occurring at the onset of his acute nephritis, persisted periodically until death about eight years later. Although the nephritis became chronic, the blood pressure and kidney function remained normal. The true cause of the convulsions became evident with the development of more definite signs of brain tumor, which proved to be a glioma of the frontal lobe (no. 8, chart 2). The seven cases of hypertensive encephalopathy recovered and are now without evidence of chronic nephritis five to 14 years later.

Hypertension was present in 53 of the 96 cases in which the blood pressure was recorded (table 4). Its occurrence was twice as frequent in the

TABLE IV

Range of Blood Pressure in 96 Cases of Acute Nephritis

	Systolic Pressure	Diastolic Pressure		
	180–200	105–200	90–100	60–85
Number of cases	10	5	4	1
	150–175	105–200	90–100	60–85
Number of cases	27	8	15	45
	100–145	105–200	90–100	60–85
Number of cases	59 *	4	12	43

* 16 cases had normal systolic and elevated diastolic pressures.

patients who were seen within two weeks of their first symptoms of nephritis as in those admitted later. This suggests that hypertension tends to occur early in the disease, and that possibly the former group were brought to the hospital earlier because of a more severe form of nephritis. The presence of hypertension was unrelated to the outcome. The general rule that a gradually rising blood pressure, or hypertension, persisting longer than a few days is an unfavorable sign in acute nephritis was borne out in the two cases in which it was applicable. One died in the acute stage; the other developed chronic nephritis. Only one of the three patients who died of uremia had hypertension, and this was minor.

Slight neuro-retinopathy consisting of edema of the disc and retina, and constriction of the retinal arteries, was observed in three cases of the series, all of which recovered.

Myocardial insufficiency, an important feature in a very small proportion of cases of acute nephritis, is at times precipitated during convulsive seizures. Cardiac failure did not, however, result from this cause in our series, although two patients had frequent severe convulsions for 24 hours before entry. Congestive failure, of moderate degree, occurred in only one case;

while dyspnea, which may have been due to left heart failure, was a symptom in three more. These four patients recovered.

All of the 100 cases had albuminuria as determined by the nitric acid test. The urinary sediments of 87 contained moderate to large numbers of red and white blood cells. In 13 there was only an occasional red blood cell during the period of observation, but more blood was probably present prior to entry to the hospital. In this clinic, the presence of red blood cell casts has been used as an important aid in distinguishing nephritis from other causes of hematuria. They were fairly constantly present in the early stage of the nephritis in the majority of the cases.

Neither the presence nor the severity of gross hematuria, which occurred in 42 per cent of the cases, was related to the outcome of the nephritis.

It is well known that renal function determined by the usual tests is of little significance in most cases of acute nephritis. This is partly due to the transient nature of the early injury in otherwise normal kidneys. During the period of anuria and oliguria the phenolsulphonephthalein excretion and urea clearance are diminished, and the blood urea nitrogen is elevated.[5, 6] This was found to be true in our series. Azotemia, present in 49 of 90 cases, was slight in most of them; and it usually occurred early in the nephritis. The blood urea nitrogen ranged from 16 to 180 mg. per 100 c.c. (table 5). The three patients who died of uremia had anuria and a urea

TABLE V

Range of Blood Urea Nitrogen in 49 Cases of Acute Nephritis with Azotemia

Milligrams per 100 c.c.	Number of Cases
16–30	22
31–40	12
41–60	7
61–90	5
120–180	3

nitrogen of more than 120 mg. per 100 c.c. The phenolsulphonephthalein excretion was determined in most of the series. The urea clearance was determined less often than the dye test, but in the cases in which both were done, the information obtained was of as little prognostic value as from the dye test alone. This may be in part explained by too infrequent use of the tests, since it is well known that it is the trend of repeated tests over a period of time, and not the single test, regardless of the kind, which gives the most useful indication of kidney function.

Late Prognosis. Most of the patients returned to the renal clinic, under the direction of Dr. O'Hare. In a few the data necessary to determine the presence or absence of chronic nephritis were obtained from the patient's physician. The criteria for complete recovery from acute nephritis consisted of normal kidney function tests, negative urine examinations and normal blood pressure. However, two cured cases, who developed hypertension about 10 years after their acute nephritis 19 years ago, have shown no evi-

dence of chronic nephritis. The blood pressure of one of them has been normal since an attack of coronary thrombosis three years ago.

Eighty-one of the 90 who survived their attack of acute nephritis have been traced. The renal status of 77, or 85.5 per cent, has been determined at periods varying from 1 to 19 years after the onset of acute nephritis (table 1). The average follow-up period was 8.7 years. Of the 13 patients whose renal condition was undetermined, nine could not be found, two had died of influenza a few months following the onset of acute nephritis, and one had died of pulmonary tuberculosis 15 years later, the renal condition being unknown. The last, who is still living after 17 years, did not respond to our inquiries. Of the 77 patients whose renal condition is known, 62, or 80.5 per cent, are cured; while 15, or 19.5 per cent, have developed chronic nephritis.

Albuminuria is the most delicate evidence of the presence of nephritis.[5] We have, therefore, as presented in charts 1 and 2, given special attention to the duration of albuminuria as a possible aid in prognosis. Of the 62 cured cases, the urine was known to have become free of albumin within two months in 14, within six months in 13, within 10 months in 4, and within a year in nine cases. The urine became albumin-free after one year in four cases; 1.5 years in one; and two years in two. The approximate time when the urine cleared in 15 patients could not be determined because of infrequent visits to the clinic. In other words, the urine became albumin-free in about half of the 62 cured cases within six months; between six months and a year in one-fifth and later than a year in one-ninth. Two patients (nos. 8 and 24, chart 1) demonstrate the significant fact that acute nephritis may heal after albuminuria has been present for two years. It is quite possible that three cases (nos. 13, 14 and 15, chart 2), now considered as having chronic hemorrhagic nephritis at 19 months in one case, and two years in the other two, may be found without evidence of nephritis in a longer follow-up study.

Of the 15 patients who developed chronic nephritis, the first 12, as shown in chart 2, were followed from 3 to 19 years. In eight of these, albuminuria in constant or increasing amounts was present on all examinations during the first year, and thereafter. Five of the eight developed chronic, hemorrhagic nephritis, and four of them were followed regularly until death. Two died in uremia five and eight years, respectively, after the onset of acute nephritis (nos. 9 and 10). The other two, whose blood pressure and kidney function tests remained normal, died of incidental causes three and four years later (nos. 8 and 12). The fifth patient (no. 1) was not seen between the first and third years after the onset of acute nephritis, but returned regularly thereafter; at 19 years albuminuria was present but the blood pressure and kidney function tests were normal. Three of the eight cases in which albuminuria was present during the first year were followed less regularly than the five discussed above. The first (no. 3) did not return after the first year; at the end of 16 years death was caused by uremia or cerebral hemorrhage. The second (no. 6) had hypertension at three years.

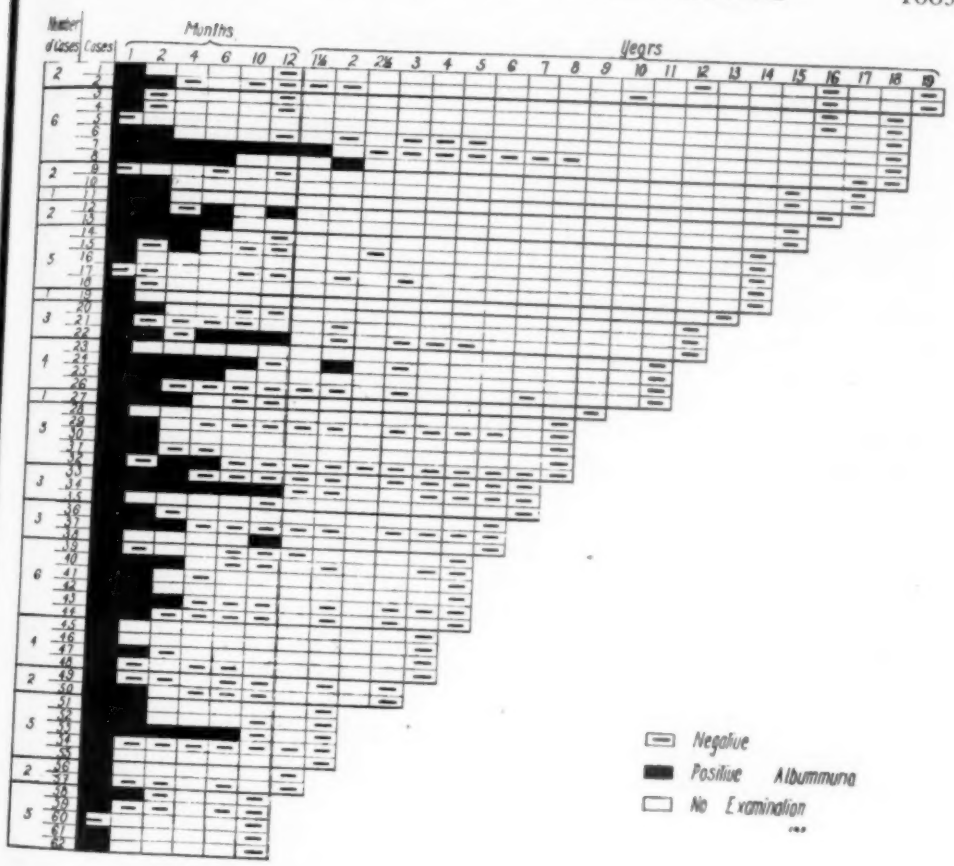
Number of cases
Cases
Months
1 2 4 6 10 12
Years
1½ 2 2½ 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Negative
Positive Albuminuria
No Examination

CHART 1. Showing urinary examinations of 62 patients who are cured of acute nephritis.

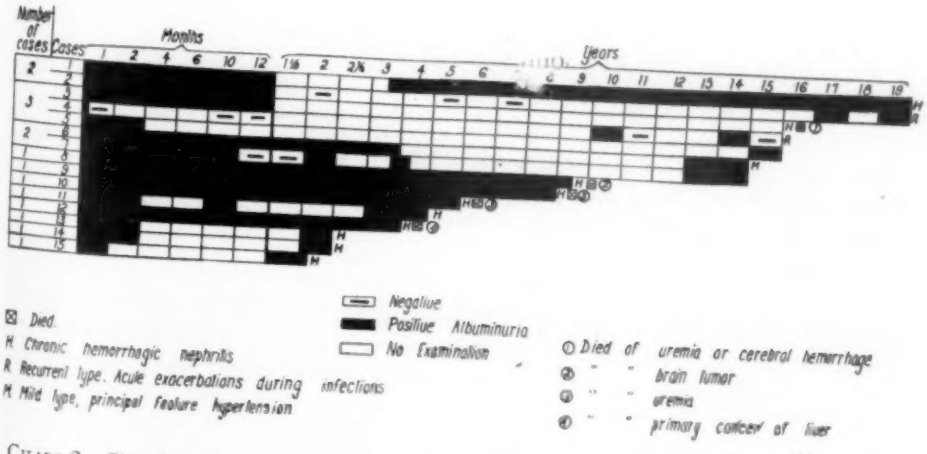
Number of cases
Cases
Months
1 2 4 6 10 12
1½ 2 2½ 3 4 5 6
Years
9 10 11 12 13 14 15 16 17 18 19
Negative
Positive Albuminuria
No Examination
⊠ Died.
H. Chronic hemorrhagic nephritis
R. Recurrent type. Acute exacerbations during infections
M. Mild type, principal feature hypertension
① Died of uremia or cerebral hemorrhage
② " " brain tumor
③ " " uremia
④ " " primary cancer of liver

CHART 2. Showing urinary examinations of 15 patients who developed chronic nephritis.

During the next nine years he was not seen at all; on his return, 13 and 14 years after the acute nephritis, the hypertension had increased. Although albuminuria and cylindruria were still present, various kidney function tests were normal. The heart was not enlarged on roentgen examination. There was moderate generalized arteriosclerosis. The third (no. 2) was not observed between the first and second years after acute nephritis. He did, however, report to us later. The urine was negative at two years, positive for albumin and casts 10 months later, negative at five and seven years, and again positive at 17 and 19 years. Kidney function tests and the blood pressure were normal at all examinations. Moderate generalized arteriosclerosis was present.

In only two of the 15 chronic cases did the urine become negative within a year, during the first month in one of them. The latter case (no. 4) was not seen from the first to the tenth year. An acute exacerbation of the chronic nephritis occurred during an acute infection of the upper respiratory tract at 10 and 14 years after the initial attack of acute nephritis. This patient would have been considered cured had he not been seen during the acute exacerbation. The other patient (no. 7) had negative urine examinations between the first and second years, but at two years albuminuria and hematuria recurred. He was treated for pulmonary tuberculosis 10 years later when there was still evidence of chronic nephritis. The tuberculosis became arrested and he is now reported to be well.

The urine studies of five cases with chronic nephritis were too infrequent to be of value in estimating the significance of albuminuria. Case 5 was observed for two months after the onset of acute nephritis; 15 years later he was reported to have albuminuria, hypertension, and cardiac enlargement. In case 11 the acute nephritis progressed into chronic, hemorrhagic nephritis; the blood pressure and kidney function tests were normal during the four years he was followed. Cases 13, 14 and 15 have chronic, hemorrhagic nephritis with normal blood pressure and kidney function tests, about two years following the initial stage.

A comparison of charts 1 and 2 shows that 80 per cent of the regularly followed cases, in which chronic nephritis developed, had albuminuria one year after the onset of acute nephritis; while only 14.8 per cent of the cured cases had albuminuria at the end of the first year or later. In other words, when albuminuria was still present at the end of a year or thereafter, the chances for progression of the nephritis into the chronic stage were approximately 6 to 1.

Significant features not given in the charts are the presence of hematuria and cylindruria, and the degree of albuminuria. Hematuria and cylindruria, often occurring in the absence of albuminuria, were important signs of renal activity, but because of their intermittent occurrence and quantitative variation, the degree and duration of albuminuria served as a more useful indication of the general trend of the course of the nephritis. In each of the 62 patients who became cured, there was either a gradual or intermittent de-

crease in the amount, or complete disappearance of the albuminuria over a period of a few weeks up to two years after the onset of acute nephritis. In the 10 chronic cases who were examined regularly during the first year, there was a slight, early decrease of the albuminuria while the patients were at bed rest, but by two months and thereafter the degree of albuminuria was constant or increasing.

In only one patient did the acute nephritis progress rapidly so that hypertension had developed by the end of one year.

The patients, in our clinic, with the nephrosis syndrome were not observed during the initial stage of their nephritis, therefore, this complication was not present in any of the cases followed in the present study.

Orthostatic albuminuria was present in only one patient, six years after the attack of acute nephritis.

Comment. A study of table 6, in which the cases of Murphy and his

TABLE VI

Statistics on the Prognosis of Acute Glomerular Nephritis in Adolescents and Adults

Author	Immediate Prognosis			Late Prognosis			
	Age Group in Years	No. of Cases	Died of Acute Nephritis, Per cent	No. of Cases in Follow-Up Study	Average Follow-Up in Years	Cured, Per cent	Became Chronic, Per cent
Murphy, Grill and Moxon	82 cases above and 12 below 11 years	94	28.7	*94	Not given	50	21.2
				*67 surviving acute stage	" "	70.1	29.8
†Murphy et al. revised	11–60	82	30.5	*82	" "	48.7	20.7
				*57 surviving acute stage	" "	70.1	29.8
McPhee and Kaye	67 cases above and 23 below 11 years	90	5.5	48	4.5 to 7.3	85.4	14.6
†McPhee revised	11–70	67	7.5	28	4.5 to 7.3	75	25
Ernberg	15–30	—	—	16	Several years	75	25
P.B.B.H. Series	12–60	100	5‡	*100	8.7	62	15
				*77§ surviving acute stage	8.7	80.5	19.5

* Calculated on basis of
† Cases arranged into group comparable to that of P.B.B.H. Series.
‡ Five other cases died of causative infection or of incidental causes.
§ Renal condition of 13 cases is unknown.

co-workers, and of McPhee and Kaye [7] have been classified into an age group corresponding to the 100 cases of the present study, shows the death rates during the acute stage of 31.7 per cent in Murphy's series, 7.5 per cent in that of McPhee and Kaye, and 5 per cent in our series. In the cases of acute glomerular nephritis in children, reported by Tallerman,[8] Guild,[9] Lyttle and Rosenberg,[10] Osman,[11] Hill,[12] and Blackfan,[13] the death rates during the acute stage ranged from 3.3 to 12.5 per cent, with an average of 6.6 per cent. The mortality, in the acute stage of war or trench nephritis, was slightly lower than in the acute glomerular nephritis of childhood, or in civilian nephritis of adults. Reports of cases of war nephritis by various authors [14 to 21] gave death rates during the acute stage ranging from 0.8 to 7.6 per cent, averaging 3.6. In the literature the greatest variation in death rates in acute nephritis was found in the reports of various small series of postscarlatinal nephritis, where the virulence of an epidemic appeared to be a factor. However, in a large series of postscarlatinal nephritis in children and young adults, reported by Hansborg,[22] the death rate was 4 per cent, and 6 per cent in a similar series of Barasch.[23] This review of the literature and the study of our cases not only bears out the opinion that the immediate prognosis in acute glomerular nephritis is good, but also shows that there is no essential difference in the death rate in children and adults, except in trench nephritis where the mortality was lower than in either children or adults in times of peace. The mortality of 28.7 per cent in the series of Murphy, Grill and Moxon is the highest found in the literature. The deaths in their series did not seem attributable to the disease which caused the nephritis.

A comparison of the late prognosis in acute nephritis of adults is also shown in table 6, in which the cases of Murphy and of McPhee and Kaye have been classified into age groups similar to that of our series. The percentage of cases in our group which developed chronic nephritis is a little lower than in the adult cases of the other authors. In acute glomerular nephritis in children, reported by various authors,[5, 6, 7, 9, 24, 25, 26, 27] the percentage of cases which became chronic varied from 0 to 16, indicating a more favorable remote prognosis than in adults. The high incidence of 51.8 per cent in the series of Patterson and Wyllie,[28] and 35.7 per cent in Osman's [11] series of children and young adults, was unexplained. The various reports of postscarlatinal nephritis gave a definitely lower incidence of progression into chronic nephritis than in nephritis of mixed etiology. In the reports of acute war nephritis,[15, 16, 18, 29, 30] the percentage of cured cases ranged from 45 to 85. The number of cases which developed chronic nephritis is difficult to evaluate because of their grouping by some authors into cases which developed chronic nephritis, cases with "residual albuminuria" without signs of nephritis, and "cases of contracted kidney with retinal and vascular degeneration." The various authors writing about war nephritis have, however, believed that a greater proportion of these cases

developed chronic glomerular nephritis than in civilian nephritis, for which a satisfactory explanation has not been given.

The present group includes both severe and mild cases of acute, diffuse, glomerular nephritis caused by various acute infections.

The only clinical observation frequently related to the ultimate outcome of the nephritis was the degree and duration of albuminuria. Similar observations described by others have rarely been expressed statistically. Brown and Evans [31] stated that the disappearance of albuminuria within a month after the onset of acute nephritis is a hopeful prognostic sign, while Tidy [32] believed that the development of chronic nephritis is usual if albuminuria persists longer than a month. Fishberg [33] makes the statement that the longer albuminuria persists the greater the chances of the nephritis becoming chronic. Murphy [1] believed that gradually diminishing albuminuria points toward a healing process. In the majority of her cured cases of acute glomerular nephritis in children, Guild found the urine cleared promptly, within two months in most cases, but that albuminuria persisted for many months in a few. Addis,[34] by use of his sediment counts, and quantitated proteinuria, has shown that in three-fourths of the cases of acute, hemorrhagic nephritis healing occurs during the first year, but complete recovery occurred as late as the fifth year.

The results in our cases suggest that when albuminuria had persisted for a year or longer after the onset of the acute nephritis, the chances of the process becoming chronic were six to one.

It should be emphasized that clinical cure of acute nephritis may not always represent cure of the underlying pathologic process. This is well illustrated by the rare case (case 4, chart 2) in which the nephritis is manifest only during exacerbations following acute infections, the urinary and kidney function studies being entirely normal in the interim. When the intervals between observations or the exacerbations are long, or if antecedent flare-ups are unknown, such a case might easily be considered cured of the initial nephritis, if not followed for a very long time. In a clinical study of this kind such a possibility cannot be eliminated.

For the purpose of this study we have considered a patient cured if there was no evidence of nephritis at the end of one year. The validity of this is borne out by the fact that of the 42 cases apparently cured at one year (average 8.7 years), only two have been found to have chronic nephritis at a later date.

Summary

Of 100 adolescents and adults with acute diffuse glomerular nephritis, 10 died during the acute stage, five primarily of their nephritis, and five of the causative infection, or of incidental causes. Eighty-one of the surviving 90 have been traced and the renal status determined in 77. Sixty-two are cured, and 15 have developed chronic nephritis during the follow-up periods, which were from 1 to 19 years with an average of 8.7 years.

The relation of the various clinical features to prognosis is discussed. The one clinical observation of greatest prognostic value was the degree and the duration of albuminuria. In the majority of the cases, disappearance or gradual and intermittent decrease in the amount of albuminuria indicated healing of the nephritis; while persistent albuminuria of a constant or increasing amount suggested progression into chronic nephritis. The results also suggest that when albuminuria (orthostatic factor excluded) persists for a year or longer after the onset of acute nephritis, the chances of the renal process becoming chronic are six to one.

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THE EFFECTIVENESS OF THE SIPPY REGIMEN IN NEUTRALIZING THE GASTRIC JUICE OF PATIENTS IF THE AMOUNT OF ALKALI IS NOT VARIED *

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THE method of ulcer treatment as suggested by Sippy is frequently used in the belief that placing the patient on the routine as outlined will effect complete neutralization of the gastric contents. Some may question the necessity of maintaining neutrality in the stomach, or may even doubt that neutrality provides optimum conditions for healing. Sippy himself, however, suggested that the absence of free acid should be used as a criterion for the effectiveness of treatment, and this conception appears to have been commonly adopted in theory. We have been unable to find in the literature any data giving hourly values for gastric acidity in patients on unmodified Sippy management. The present study has been undertaken to determine how often the unmodified regimen will bring about complete neutralization.

METHOD OF STUDY

A representative group of 55 patients with peptic ulcer has been studied. Forty-six were suffering from duodenal and nine from gastric ulcer. Their ages varied from 20 to 70 years; the average age for the entire group being 44 years. Forty-eight were males and seven females. All of the patients were having symptoms of peptic ulcer at the time of entrance into the hospital. All but one showed a typical deformity with the roentgen-ray; and in most instances, a crater was demonstrated fluoroscopically. The one exception had such a typical history that the diagnosis of peptic ulcer seemed definite in spite of the negative roentgenographic studies. Because the number of gastric ulcers is small, we did not include them in our data. However, the findings in these patients were similar to those obtained in cases of duodenal ulcers.

No postoperative cases were used because of the difficulty encountered in determining the site of the tube in the stomach. Furthermore, it was thought that the data obtained on postoperative stomachs might be misleading in so far as the purposes of this study are concerned.

Patients were placed on the routine treatment as outlined by Sippy. They were started on 90 c.c. of equal parts of whole milk and 20 per cent cream on the hour, from 7 a.m. to 7 p.m. They were given a powder consisting of calcium carbonate (0.6 gm.) and sodium bicarbonate (2.0 gm.)

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From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.
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on the half hour. This procedure will be referred to in the remainder of the paper as the "first day Sippy." Increasing amounts of food were given in the succeeding days so that by the seventh day, patients were also receiving six small feedings of soft eggs, cereals, toast, crackers, butter, and jellies at two hour intervals. Studies were made on the first or second day after the patient was taking all six feedings. This period of study will be later referred to as the "seventh day Sippy." Two weeks later the diet was changed to the so-called "fourth week Sippy." Three small meals were substituted for the six feedings. Milk and cream and powders were continued as before. These meals included a wide variety of foods, although all vegetables and fruits were either strained or pureed. Relishes and highly seasoned food were forbidden. The patients were allowed out of bed and were encouraged to engage in as much activity as ward life would permit.

The patients were studied on the "first day," "seventh day," and "fourth week" periods. Because many physicians have disapproved of giving the amounts of alkali required by the Sippy regimen on the grounds that it tends to increase the production of hydrochloric acid and, therefore, defeats the purpose of the treatment, as well as producing alkalosis on occasion, we have also determined the effect of taking milk and cream without powders. Unless the patients were extremely ill, this procedure was carried out before the Sippy regimen was begun. This was done to avoid the possible cumulative effect of previous alkalies on the gastric response.

The routine on the days of study was as follows: a Levine tube was passed at 7 a.m. and the total fasting secretion was removed. Five c.c. specimens were withdrawn at intervals of 30 minutes throughout the day, just prior to the administration of milk or powders. The specimens were examined promptly after removal. It was found that the presence of bile could be traced in most instances to one of two causes. Either the tip of the tube had slipped into the duodenum, or bile had been regurgitated as a result of nausea and retching. We, therefore, discarded all those specimens which contained bile, although in some instances this may have been the result of normal regurgitation from the duodenum. However, it seemed that this rule would result in more accurate data.

All specimens were analyzed in the usual manner for free and total acidity, using Töpffer's reagent and 1 per cent alcoholic phenolphthalein respectively. One observer (P.H.W.) performed all the titrations with tenth normal sodium hydroxide, and the results are expressed in the number of c.c. of a decinormal solution of sodium hydroxide required to neutralize 100 c.c. of gastric juice. (Clinical units.)

Data and Discussion

Chart 1 shows the results of 30 determinations made when the patients were taking milk and cream, and 46 determinations on patients taking the "first day Sippy." The free acidity was somewhat higher with only

milk and cream (an average of two clinical units) than if the alkaline powders were added. A comparison of the curves obtained on patients taking only milk and cream with those obtained when patients were taking the " seventh day " and " fourth week " management (charts 2 and 3) shows

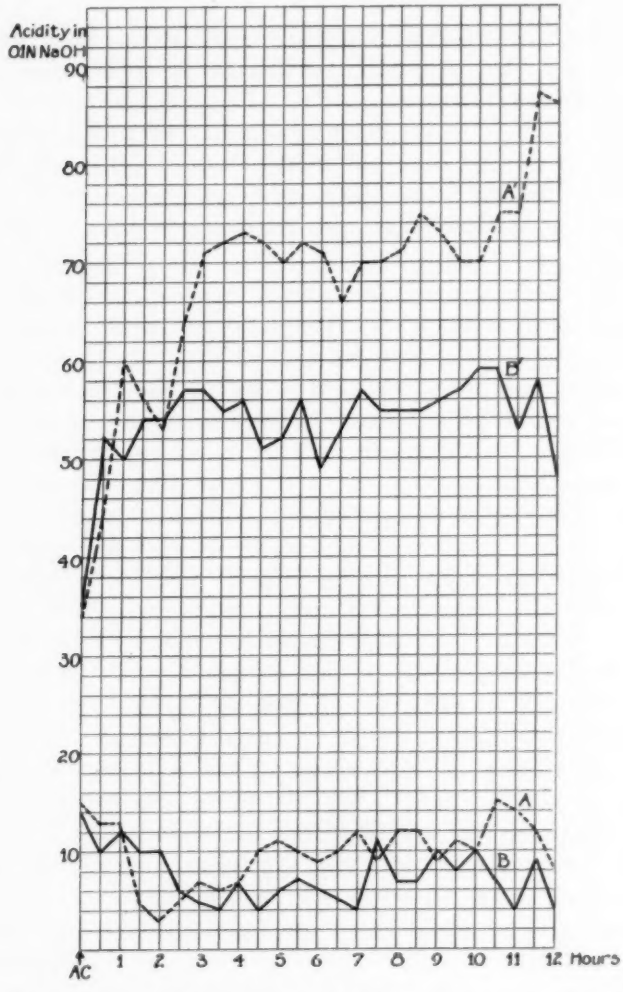

CHART 1. Free and total acidity curves on 30 patients who were given hourly feedings of milk and cream (A and A') and on 46 patients who, in addition to the milk and cream, were given calcium carbonate 0.6 gm. and sodium bicarbonate 2.0 gm. and on the half-hour, the first day Sippy regimen (B and B').

that, at no time, did the giving of alkali increase the amount of free acid present.

Chart 2 compares the results of the " first " and the " seventh day " diets. The free acidity in the latter was distinctly lower. It was zero part

of the time and only on a few occasions rose above four. This drop in the free acidity was probably due to the longer period of rest (often two weeks), the combining power of the food for acid, and the ease with which these soft

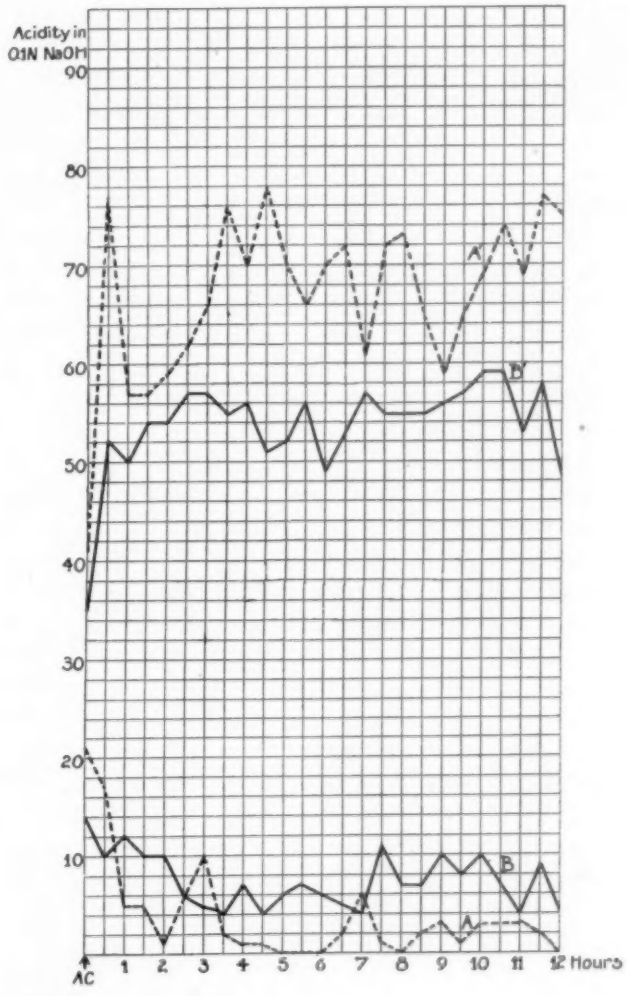

CHART 2. Free and total acidity curves on 46 patients who were given the first day Sippy regimen (B and B') and 14 patients taking the seventh day Sippy regimen (A and A').

foods passed from the stomach. That an increase in the amount of acid was present may be seen by the total acid curve.

Chart 3 shows that the average free acidity was distinctly higher in the "fourth week" than on the "seventh day," and was somewhat higher than on the "first day Sippy." This increase in the free acidity accompanies greater activity on the part of the patient as well as the wider variety of

foods. Because Sippy recognized this fact, he included the " fourth week " in his regimen, thus enabling him to overcome any higher values of acidity by changing the size of the powders. The curve for the total acidity was much the same as on the " seventh day."

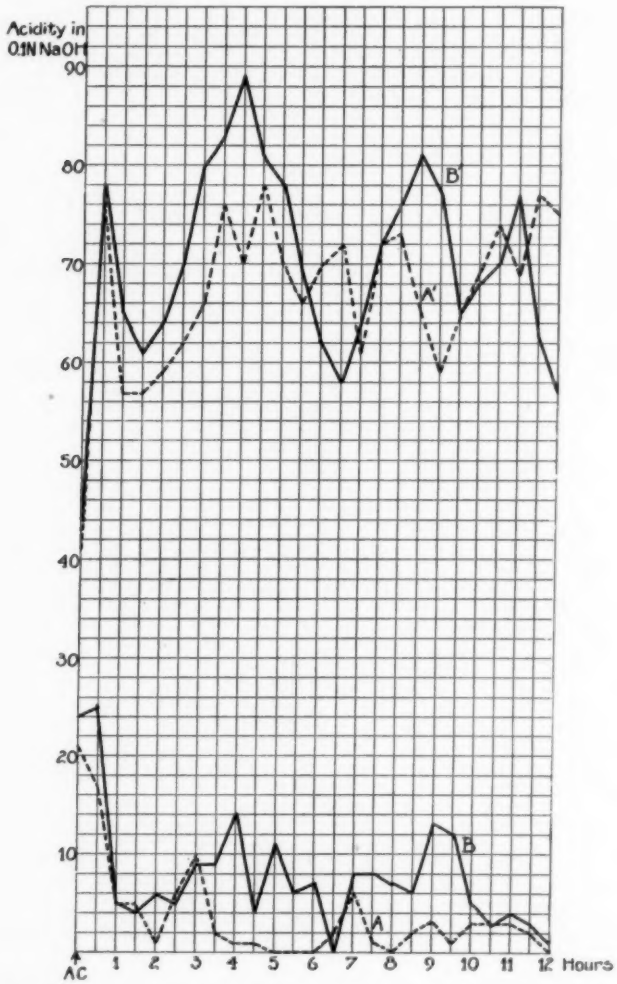

CHART 3. Free and total acidity curves on 14 patients on the seventh day Sippy regimen (A and A') and 14 patients on the fourth week Sippy regimen (B and B').

Although control of the free acidity is presumably the important factor of the Sippy treatment, the values for the total acidity have been given on the charts. It is seen that the total acidity was the same in all instances except on the first day that alkaline powders were instituted, where the readings average 14 points lower. This may be seen on chart 1. Because of the relatively large amount of data accumulated, we thought it might be

interesting to calculate the effectiveness of the alkalies, using the total acid determination as a basis without considering the free acid. Thus, if we assume that the stomach secretes approximately 1500 c.c. of juice daily, or about 50 c.c. per hour, with a total acid value of 150 clinical units, the hourly secretion of hydrochloric acid will be 7.5 milli-equivalents (274 mg.). The amount of sodium bicarbonate required to neutralize this amount of acid can be calculated as 630 mg. Actually the average value for total acid was lower by only 14 clinical units on the days of alkali administration than on control days with only milk and cream. (Chart 1.) This is a difference of 0.7 m.eq. of acid hourly, while the alkali given amounted to 35.0 m.eq. hourly. In other words, on the average, 50 times more alkali was given than was actually used for purposes of neutralization. However, it may be maintained that the hourly secretion rate is higher where ulcers are found. Assuming, then, a secreting rate of 100 c.c. per hour, we still find that 25 times more alkali was used than should have been necessary in the neutralization process. These average values, however, are perhaps misleading since a wide variation in effectiveness was encountered as may be noted from table 1. But it seems clear that the majority of patients require amounts of alkali greatly in excess of that which is needed to neutralize the maximum amount of acid, which we believe the stomach to be capable of secreting.

There are two explanations for the fact that the amount of alkali required is much larger than the theoretical value calculated from the estimated rate of gastric secretion. The alkali may induce a more rapid emptying of the stomach, or may stimulate gastric secretion. Both possibilities should be considered. It seems probable, however, that rapid emptying is the more important.

Since these charts did not show the effect of the treatment on individual cases, table 1 has been included. The patients were divided into four groups as follows: Group 1 shows the percentage of cases which were completely controlled, i.e., those exhibiting no free acid during the day of the test; Group 2 includes those patients whose acidity never went above 10; Group 3 includes those patients whose acidity occasionally went above 10, but never

TABLE I

Showing the Relative Percentages of Effectiveness of Milk and Cream and Various Stages of the Sippy Treatment on the Gastric Acidity

Group	Gastric Acidity in Terms of 0.1N NaOH	Per cent of Cases			
		Milk and Cream	First Day Sippy	Seventh Day Sippy	Fourth Week Sippy
1	No free acidity	7%	10%	14%	7.1%
2	No reading over 10	10%	13%	7%	7.1%
3	No reading over 20	16.6%	13%	35.7%	28.5%
4	One or more readings over 20	66.6%	63%	42.8%	57%

over 20; and, Group 4, those patients whose acidity was above 20 on at least one occasion. The table shows again that the best results were obtained on the " seventh day " and that in general, the results on the " fourth week " were similar to the " first day."

We have classified as adequately controlled: (1) those showing no free acid, (2) those showing free acid (below 20 clinical units) on not more than three occasions, provided the acidity did not occur in consecutive specimens, and (3) those having readings above 20 on one occasion but completely controlled the rest of the time. On this basis, 54 per cent were adequately controlled on the " first day," 71 per cent on the " seventh day," and 57 per cent on the " fourth week Sippy." These figures indicate that only a little more than one-half of the patients were controlled without any attempt being made to vary the size of the powders. Sippy recognized the importance of individual variations, for he states, " Control of the free hydrochloric acid should be maintained from the beginning," and he adds later, " It should be understood, however, that the presence of free hydrochloric acid now and then for a few minutes each day may not seriously interfere with the healing of the ulcer."

Since it would be of value to know before treatment is instituted in which patients adequate control can be expected, we tried to correlate the results of treatment with the fractional gastric analyses that were performed in all cases before the patient was placed on treatment. Fifty c.c. of 8 per cent alcohol were used as a test meal. The number of patients that were adequately controlled was then compared with the results of the gastric analyses, using the highest reading of the free acidity as the index. Adequate control occurred in all patients whose free acidity did not go above 20 at the time of the analysis. For those patients in whom the acid went above 20, the number of those adequately controlled fell markedly. It seemed to make little difference how far above 20 the acidity went. Fifty per cent of those patients whose acidity fell between 20 to 40 were controlled, 64 per cent of those between 40 to 60, and 65 per cent of those above 60. Since the number of cases in which the acidity remains below 20 is small, gastric analyses are of little aid in determining which patients will be controlled by the regimen. An attempt to use the average for all determinations of the gastric analysis as an index was found to be even less satisfactory.

We are unable to say what effect the continuous presence of the tube in the stomach may have had on these values. It is probable that the annoyance and discomfort, which the presence of the tube entails, would decrease the gastric response.

The treatment, as used, abolished all symptoms in all patients, usually by the second day and without exception by the fourth day. There appeared to be little difference in the clinical response of those patients in whom the acid was satisfactorily controlled as compared with those in whom adequate neutralization was not obtained. The present series is too small to permit an accurate estimate of the relationship between symptomatic relief

and effectiveness of acid neutralization, and we do not wish to enter upon that controversy at present. We can only say that in the present series no such relationship was apparent. The slight difference between the acid values on milk and cream alone and those when alkalies were added is significant in this connection; our data indicate that the addition of alkali to hourly milk and cream feedings produces but little decrease in free acid. This phase of the problem should be studied further.

We feel that the results here presented are helpful in understanding what is accomplished by alkali therapy in ulcer. Because the control was not absolute in all cases, we should not question the large amount of clinical experience which has demonstrated the effectiveness of alkali therapy in peptic ulcer.[3] It does suggest that a more efficient regimen might be developed, and emphasizes that each patient should be considered individually.

Summary

1. Forty-six patients with duodenal ulcer received the routine Sippy treatment. Specimens of gastric contents were removed every half hour from 7 a.m. to 7 p.m. and the free and total acid determined when only milk and cream were given and on days corresponding to the " first day," " seventh day," and " fourth week " procedures of Sippy.

2. The treatment given abolished symptoms in all cases.

3. The free acidity was adequately controlled in more than one-half of the patients, even though no variations were made in the amount of alkali given.

4. The data show that if the free acidity does not rise above 20 after an alcohol test meal, the patient will obtain adequate control by this treatment. There seem to be no criteria to determine which patients will be controlled in the larger group whose free acidity goes above 20 following an alcohol test meal.

5. Calculations suggest that 25 to 50 times more alkali was given than should be necessary theoretically.

6. If a routine treatment is used, one can be assured of complete neutralization only if frequent aspirations are performed.

THE VALUE OF A MIXTURE OF POWDERED MILK AND ALKALI FOR NEUTRALIZING THE GASTRIC ACIDITY OF PATIENTS WITH PEPTIC ULCER *

By PAUL H. WOSIKA, M.D., *Chicago, Illinois,* and EDWARD S. EMERY, JR., M.D., *Boston, Massachusetts*

SINCE Sippy introduced his method of treating patients affected with peptic ulcer, there has been no unanimity of opinion among the medical profession concerning its therapeutic value. Those who oppose the treatment do so largely on the ground that large amounts of alkali are contraindicated, and that the results do not justify the time and trouble which the treatment entails. Its enthusiastic advocates maintain that complete neutralization of the gastric contents can be obtained if the treatment is carried out properly and that better results will follow this therapy. They argue that the poor results claimed for the therapy by others follow a failure to administer the treatment properly.

Recent studies of the disease teach us that the important essentials of treatment consist of control of the gastric acidity and of debilitating influences such as fatigue, emotion and infection. The best form of treatment will control these factors, and the Sippy therapy is suited best for neutralization of the gastric contents. Unfortunately the frequent feedings, which are the only sure way to obtain neutralization, constitute in the opinion of all a serious objection to this mode of treatment. Patients dislike the bother of taking something every half hour and in many instances will not follow the regimen carefully or thoroughly enough to accomplish its purpose. To meet this objection many physicians are prone to introduce so-called modifications which so alter the efficacy of the treatment as to do away with whatever advantages it may possess over other therapeutic procedures. These modifications appear justified because frequently they will relieve symptoms as quickly and completely as Sippy's published regimen. But early relief from pain is a disadvantage, if it misleads the patient and physician into a false idea that healing is taking place with the result that other important aspects of treatment are ignored. Hence one must condemn modifications whose sole object is to provide relief. But a modification that will retain the value of the Sippy treatment and at the same time eliminate many feedings will be a distinct advantage. We are therefore suggesting a modification which seems to fulfill these requirements.

In the spring of 1933 one of our patients inquired about the justification of adding the prescribed Sippy powders to his milk. He believed that this procedure gave him a longer period of relief and that he did not require

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From the Medical Clinic of the Peter Bent Brigham Hospital. The expenses of this study were defrayed by the Upjohn Company.

medication every half hour. Therefore, we decided to investigate the effect of powdered milk on the gastric juice, for, if this could be substituted for whole milk and cream, it would be a simple way for a patient to take an alkalinized milk product. This paper compares the effect on the gastric acidity of an alkalinized powdered milk with the effect of a routine Sippy regimen.

Method of Study and Data

We have already prepared a detailed account of the method of investigation.[1] To summarize it, we studied 46 patients with duodenal ulcer. A stomach tube was passed in the morning and allowed to remain in the stomach for 12 hours while 5 c.c. of gastric contents were withdrawn every half hour. One observer (P.H.W.) performed all titrations for the free and total acidity in the usual manner, using Töpffer's and 1 per cent phenolphthalein solutions as indicators. The patients were studied at various stages of the routine Sippy regimen: namely, the first day, seventh day, and fourth week. We also investigated the effect of milk and cream without powders. Next we determined the effect on the same patients of a commercial preparation of powdered milk. For this purpose we used 12.5 gm. of "Klim" or "Parlac" mixed with 90 c.c. of water. According to the formula given for these products, patients received from 12.5 gm. of the product approximately 4.75 gm. of carbohydrate, 3.33 gm. of protein, 3.5 gm. of fat, with a total caloric value of 64. Ninety c.c. of the mixture of milk and cream ordinarily used in the Sippy treatment contain 4.27 gm. of carbohydrate, 2.6 gm. of protein and 10.12 gm. of fat, with a total caloric value of 118.56. The commercial preparation afforded 22.1 per cent more protein, 65.5 per cent less fat, and about half as many calories.

The effect on the gastric acidity of using 90 c.c. of whole milk and cream is compared in chart 1 with the effect of 12.5 gm. of powdered milk. The chart shows that the results are quite similar with both preparations, although with the powdered milk, the free acidity drops toward the end of the day to a level slightly below that obtained with whole milk and cream. The total acidity was much the same in both instances. These figures convinced us that 12.5 gm. of powdered milk controlled the gastric acidity as successfully as 90 c.c. of milk and cream.

The next step was to compare the effect of an alkalinized powdered milk with the usual Sippy treatment. Therefore, we mixed 0.6 gm. of calcium carbonate and 2 gm. of sodium bicarbonate (the dose with which Sippy initiated treatment) with the 12.5 gm. of powdered milk, and the entire mixture was given to the patient in 90 c.c. of water. This was repeated every hour. This method, if successful, would decrease the number of medications from approximately 29 to 14.

The results of this procedure, as compared to those with the routine Sippy, are shown in charts 2, 3, and 4. Chart 2 shows the average of 46 determinations on the first day Sippy. Water was allowed in small quanti-

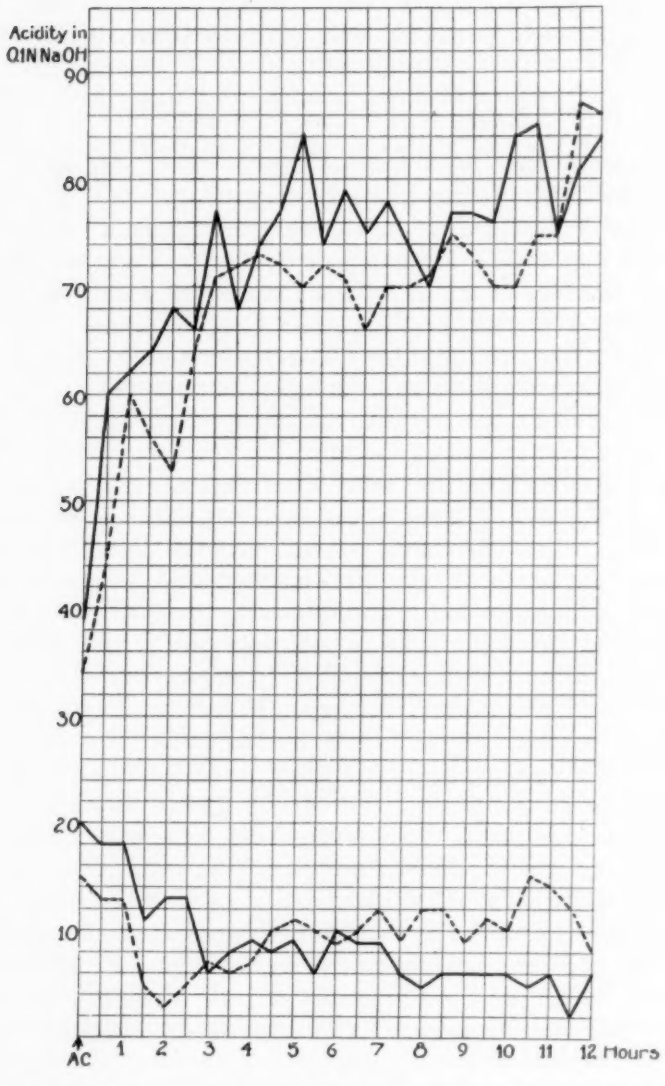

CHART 1. Shows the average free and total acid curves of plain powdered milk (12.5 gm.) (solid line) on 28 patients, compared with milk and cream (90 c.c.) (broken line) on 30 patients.

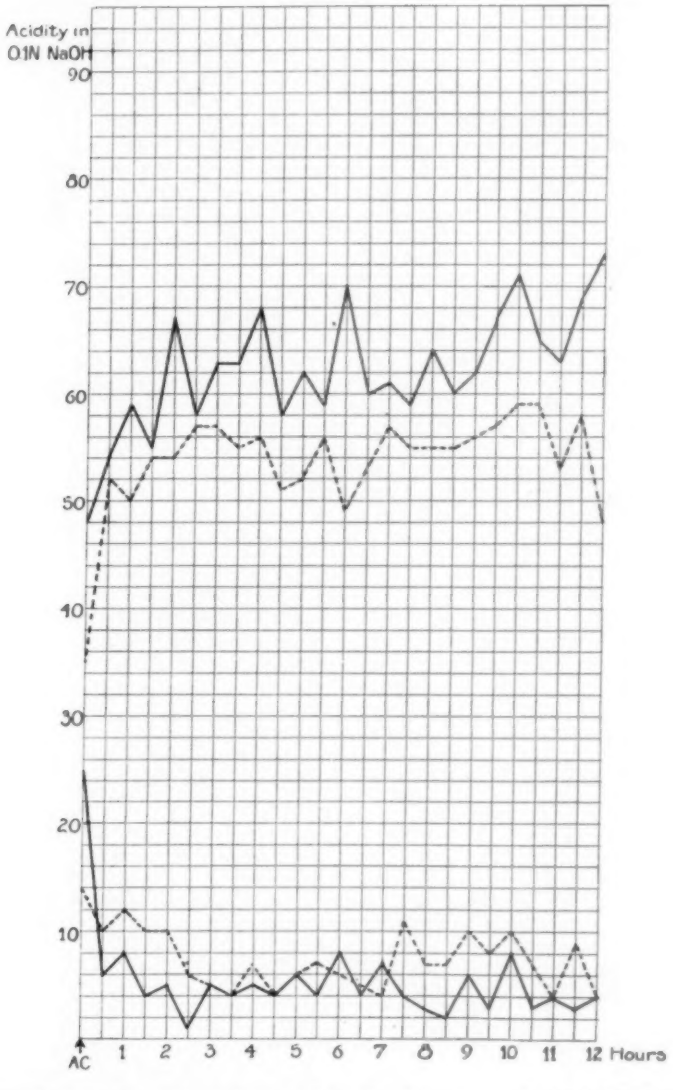

CHART 2. Shows the average free and total acid curves of alkalinized powdered milk (12.5 gm. plus one Sippy powder) (solid line) on 45 patients compared with the routine first day Sippy (broken line) on 46 patients.

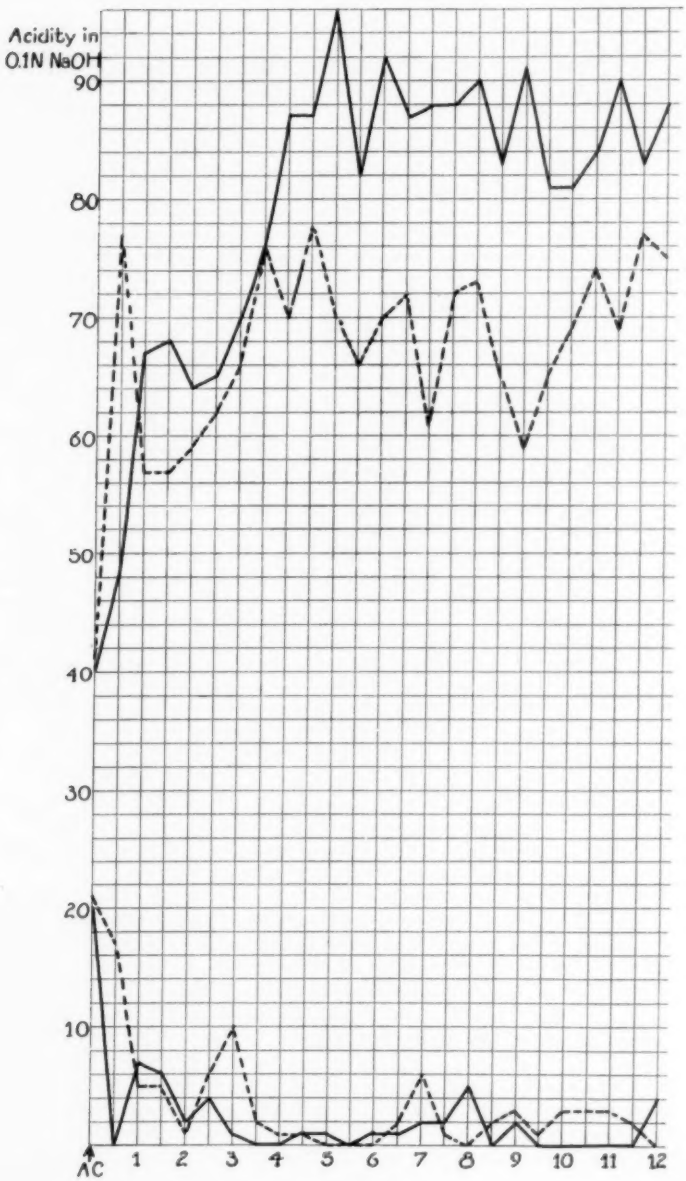

CHART 3. Shows the average free and total acid curves on the routine seventh day Sippy (broken line) on 14 patients, compared to hourly alkalinized powdered milk and 6 small feedings (solid line) on 17 patients.

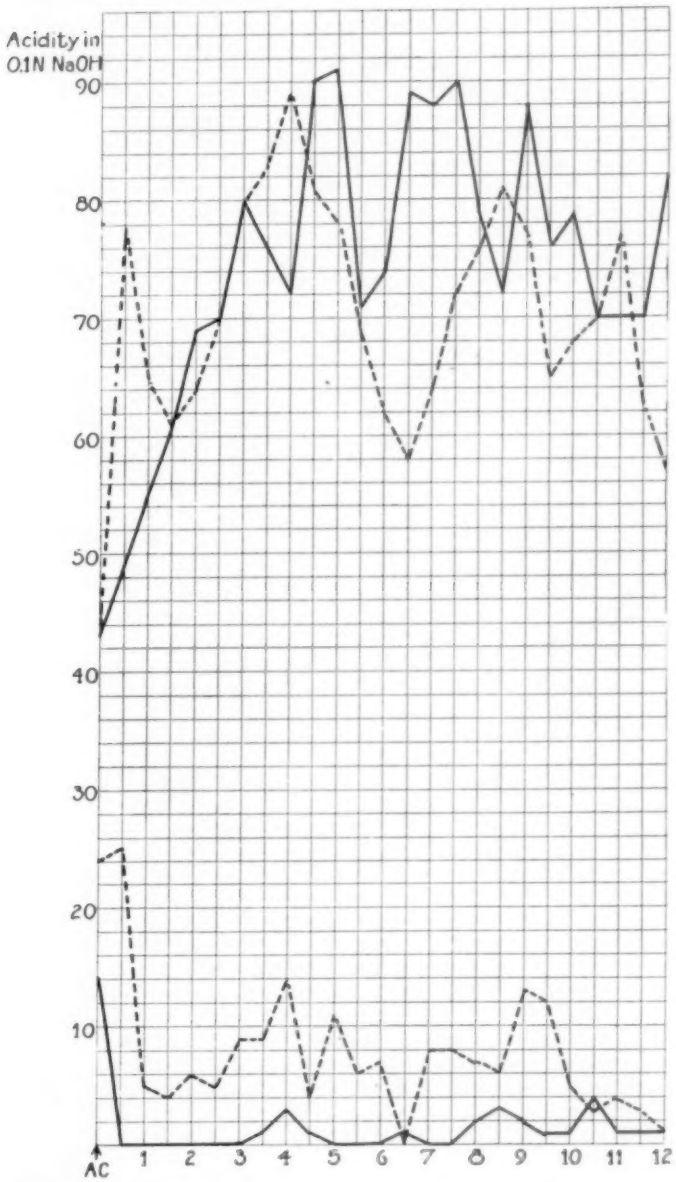

CHART 4. Shows the average free and total acid curves on the routine fourth week Sippy (broken line) on 14 patients, compared with the same feedings but using alkalinized powdered milk (solid line) on 17 patients.

ties, usually in the form of cracked ice in addition to the milk and alkalies. The free acidity remained low under both methods. The curve for total acidity was the same whether whole milk and cream or powdered milk was used. It is interesting to note that the total acidity was less when no alkali was given (compare with chart 1).

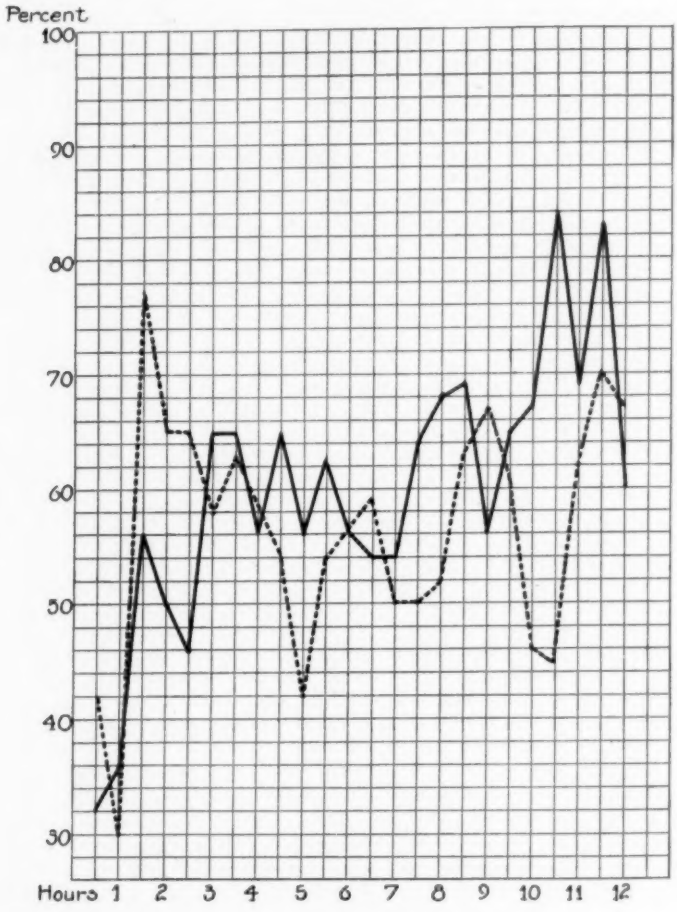

CHART 5. Shows the percentage of patients who had no free acid using powdered milk (solid line) on 28 patients and milk and cream (broken line) on 30 patients for half hour periods in 12 hours.

Chart 3 shows the effect of both treatments on the seventh day, at which time the patients were receiving six small feedings in addition to the milk and alkalies. Observations were made on 14 patients who were receiving whole milk and cream with powders on the half hour, and 17 patients who were taking the alkalinized milk powder. The curves for both free and total acidity are virtually identical. The total acidity has again risen to the same level that existed before alkalies were started.

The results obtained on patients in the fourth week of treatment are shown in chart 4. The patients were receiving the same kind of treatment as on the seventh day, with the exception that the six feedings had been changed to three meals. They were encouraged to be up and around the wards in order to approximate as closely as possible the conditions under which they would live after leaving the hospital. The chart shows that

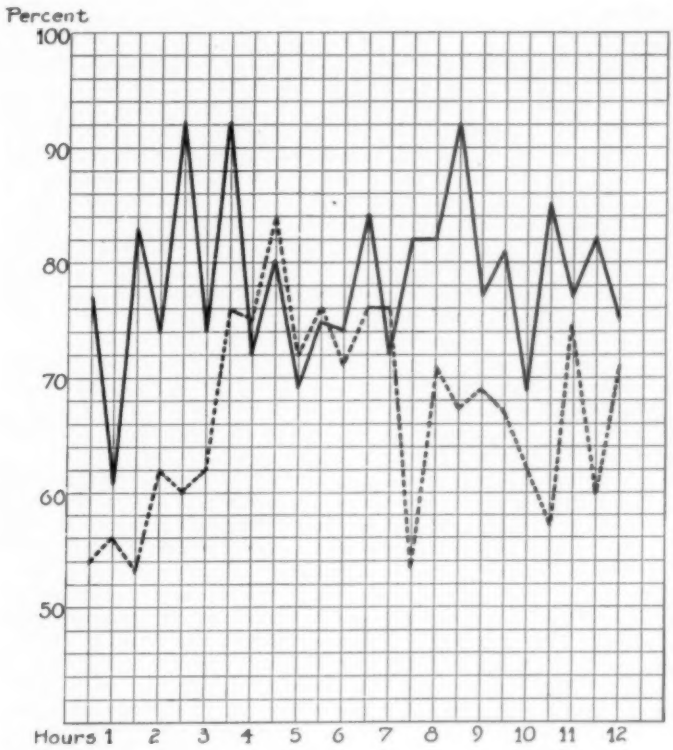

CHART 6. Shows the percentage of patients who had no free acid when alkalinized powdered milk (solid line) was used on 45 cases and the routine first day Sippy (broken line) was used on 46 patients.

hourly feedings of alkalinized milk powder controlled the gastric acidity about as well as whole milk and cream with powders given on the half hour.

Although these charts show the average effect on all the patients by the milk and powders and alkalinized powdered milk, they give no clue as to the effect on the individual patient. Therefore, charts 5, 6, 7, and 8 are included to show the percentage of patients who showed no free acid for each half hour throughout the day. It is seen that the alkalinized powdered milk reduced the gastric acidity to zero in a much higher percentage of instances than the routine Sippy treatment.

In our previous report we discussed the efficacy of the routine Sippy procedure in producing adequate control of the gastric acidity. Included as being adequately controlled were: (1) Patients whose gastric contents never showed free acid during the 12 hours of observation. (2) Patients in whom the gastric contents showed free acidity of not more than 20 and was not found on more than three occasions provided this finding did not occur in consecutive specimens. (3) Patients in whom the gastric contents

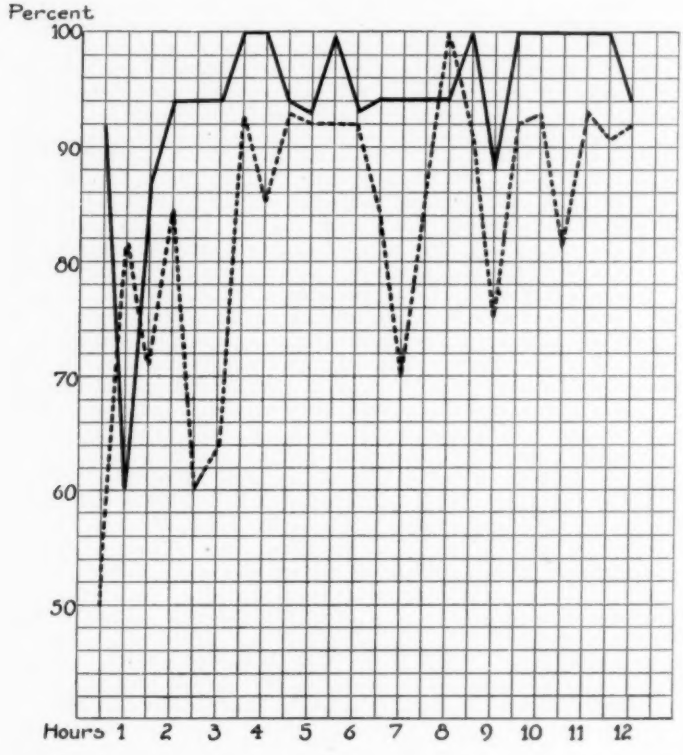

CHART 7. Shows the percentage of patients who had no free acid using alkalinized powdered milk plus 6 additional feedings (solid line) on 17 patients and the routine seventh day Sippy (broken line) on 14 patients.

showed a reading above 20 on one occasion, but were completely controlled the rest of the time.

This classification gives us a means of comparing the efficacy of the routine Sippy treatment with the alkalinized powdered milk. Table 1 shows that 90 c.c. of milk and cream and powdered milk without alkali were equally efficacious. Milk and cream adequately controlled 47 per cent of the patients, compared to 50 per cent on powdered milk. However, when alkalies were added, the alkalinized powdered milk gave much more satisfactory results. On the first day, 75 per cent were adequately controlled with

alkalinized powdered milk to 54 per cent by the routine Sippy. On the seventh day, the figures were 94.1 per cent by alkalinized powdered milk to 71 per cent by the routine Sippy, and on the fourth week, 94.1 per cent to 57 per cent.

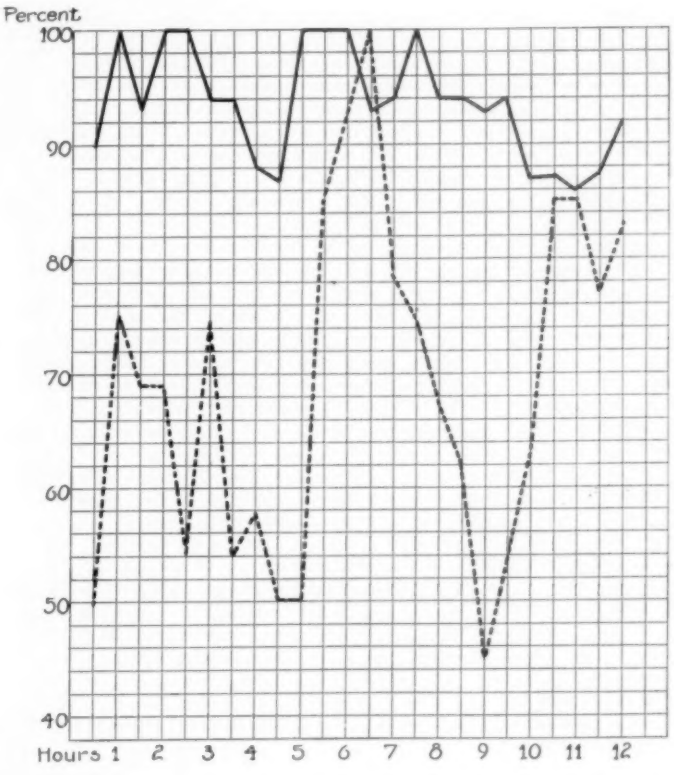

CHART 8. Shows the percentage of patients who had no free acid using alkalinized powdered milk and three meals (solid line) on 17 patients and the routine fourth week Sippy (broken line) on 14 patients.

DISCUSSION

These results were more satisfactory than we had expected. The most we had hoped for was a method which would simplify the treatment of the patient without sacrificing its efficiency. According to the present observations, the method is even more efficient as a means of neutralization than the usual procedure.

We have no data that explain the greater efficiency which the alkalinized powdered milk seems to possess. A greater dilution would lower the titratable acidity, but even less fluid was given by this method than the ordinary Sippy. It is hard to estimate what effect a difference in flavor might have. Most of the patients enjoyed the whole milk and cream better than the powdered milk. This became more pronounced when the patients

TABLE I

Showing the comparative results of milk and cream and routine Sippy procedures with powdered milk with similar feedings expressed in per cent. Although the number of medications is one-half when powdered milk is used, the percentage of adequately controlled patients is seen to be higher.

Group	Classification of Patients by Amounts of Free Acid Present	Procedure with Milk and Cream	Procedure with Powdered Milk
		Percentage control of 30 patients using milk and cream without alkalies	Percentage control of 28 patients using powdered milk without alkalies
1	No free acid	7	10.7
2	No reading over 10	10	7.1
3	No reading over 20	16.6	21.4
4	One reading over 20	66.6	60.7
	Adequate control	47	50
		Percentage control of 46 patients using the first day Sippy regimen	Percentage control of 44 patients using alkalinized powdered milk once an hour
1	No free acid	10	34
2	No reading over 10	13	4.5
3	No reading over 20	13	22.7
4	One reading over 20	63	38.6
	Adequate control	54	75
		Percentage control of 14 patients using the routine seventh day Sippy	Percentage control of 17 patients using alkalinized powdered milk with six additional feedings
1	No free acid	14	47
2	No reading over 10	7	11.7
3	No reading over 20	35.7	17.6
4	One reading over 20	42.8	23.5
	Adequate control	71	94.1
		Percentage control of 14 patients using the routine fourth week Sippy	Percentage control of 17 patients using alkalinized powdered milk with three meals
1	No free acid	7.1	47
2	No reading over 10	7.1	23.5
3	No reading over 20	28.5	5.9
4	One reading over 20	57	23.5
	Adequate control	57	94.1

knew that it was powdered milk. However, it does have a flatter taste. A smaller " appetite secretion " might, therefore, result. On the other hand, the addition of three meals a day, which the patient received on the " fourth week " diet, not only failed to increase the amount of free acidity, but the patients were controlled more completely. The failure of the usual foods

to stimulate a greater secretion of acid argues somewhat against the idea that the "appetite secretion" made much difference. The greater amount of protein in the powdered milk should decrease the amount of free acid by increasing the amount of neutralization. As already pointed out, the powdered milk provided about one-fifth more protein than the milk and cream. It was also noted that the milk curds obtained in the samples were smaller with the powdered milk than with the whole milk. This suggests, of course, that the protein in the powdered milk could neutralize the acid more effectively.

Another observation makes us feel that the increased amount of protein is an important factor in the greater degree of neutralization. If we increased the amount of milk powder to patients whose acidity was not entirely neutralized by the 12.5 gm. dose, there resulted an increased degree of neutralization comparable to the greater effectiveness which seemed to exist with the alkalinized powdered milk over the ordinary Sippy. This difference could not be explained by the difference in "appetite secretion." Therefore, we feel that even though a difference in flavor may play some rôle, the alkalinized milk powder is more effective as a neutralizing agent.

This method of treatment has certain practical advantages. Mixing the dried milk with the alkaline powders overcomes the necessity of a patient carrying both fresh milk and powders. It also decreases the number of medications by one half, which is a distinct advantage to the patient who works. Finally, it costs somewhat less than if equal parts of whole milk and 20 per cent cream are taken, provided a non-advertised brand of powdered milk is purchased.

Among its disadvantages may be listed the taste, which is not pleasant to one unaccustomed to it. However, the taste is largely a matter of habit, and patients will overcome this objection in a short time. Moreover, a failure to stimulate secretion by the absence of flavor really is an advantage. The fewer number of calories which the powdered milk supplies can be taken care of easily by increasing the other simple foods allowed in the diet. Its greatest disadvantage is the difficulty of mixing the powder with the water. It tends to adhere to the glass and requires much stirring to obtain a smooth mixture. But we hope to circumvent this disadvantage by having the mixture made into tablets.

We do not wish to suggest this treatment as a substitute for the Sippy regimen, the object of which is to neutralize adequately the gastric acidity of every patient with ulcer. A physician can be sure of adequate neutralization only if he performs frequent aspirations and increases the amount of alkali to those patients who require it. No method of therapy which utilizes a fixed amount of milk and cream and alkali can be expected to neutralize completely the gastric juice of all patients. We feel that this method is a distinct advantage for those physicians who utilize the routine Sippy treatment, but for one reason or another do not attempt to secure complete neutralization.

More recent studies demonstrate that complete neutralization is not an essential requirement for healing. Many ulcers heal spontaneously in the normal course of events without any treatment. Those experiments which incriminate the acid as a cause of ulcers depend upon the prevention of all neutralization by duodenal regurgitation, which suggests that the development of an ulcer may follow from an interference with this normal means for regulating the acidity. The use of an alkalinized milk powder at hourly intervals should neutralize the gastric acidity as effectively as duodenal regurgitation. Continued use of such a regimen should, therefore, regulate the stomach contents in such a way as to prevent the development of unusual degrees of acidity. The change in the incidence of feeding from half hourly to hourly intervals will permit a much larger group of individuals to carry out this simplified regimen.

SUMMARY

It has been found that 12.5 gm. of a preparation of powdered milk mixed with the usual Sippy powder containing 0.6 gm. of calcium carbonate and 2.0 gm. of sodium bicarbonate, and given at intervals of one hour, are somewhat more effective in neutralizing the gastric acidity than 90 c.c. of milk and cream and the same powder given in the usual way advised by Sippy.

REFERENCE

1. WOSIKA, P. H., and EMERY, E. S., JR.: The effectiveness of the Sippy regimen in neutralizing the gastric juice of patients if the amount of alkali is not varied. (See p. 1070 in this issue of the ANNALS.)

STUDIES IN HYPERTENSION; A PROPOSED CLASSIFICATION OF HYPERTENSION BASED UPON THE NITROGEN DISTRIBUTION OF THE SERUM PROTEINS *

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IN a previous publication [1] we reported that experimental hypertension in rabbits produced by the injection of a mono-amino acid (aspartic acid) is associated with definite alterations in the nitrogen distribution of the serum proteins. These changes are an increase in the mono-amino nitrogen and a decrease in the basic amino nitrogen with a resultant change in the ratio between these two fractions (referred to as the M/B ratio). We have noted in further studies similar changes in the nitrogen distribution of the serum proteins in hypertension in man. Since these changes offer a basis for the classification of hypertension, the results of this investigation are reported in this paper.

Methods. The blood pressure readings were obtained either with the sphygmotonograph or a mercury manometer. The procedure for taking the blood specimens, the separation of the serum proteins and the technical methods for the analysis of the blood protein fractions have been described in detail elsewhere.[2] The amide and humin nitrogen were both removed before the other fractions were determined; consequently, they are of no significance in the present discussion.

EXPERIMENTAL RESULTS

Normal Values. Table 1 shows the nitrogen distribution of the serum proteins in a group of 20 normal adults, most of whom were hospital interns between 21 and 30 years of age, the average being 26 years. The systolic blood pressure varied between 104 and 135, the average pressure being 117. The diastolic pressure ranged between 50 and 95, with an average of 76. The pulse pressure varied between 28 and 56, with an average of 41. All of the group were free from renal, cardiac, and metabolic disturbances.

In this group the total nitrogen varied between 420 and 700, with an average of 532 mg. per 100 c.c. blood. The basic amino nitrogen varied between 100 and 190, with an average of 140 mg. In only one instance was it as low as 100 mg., while in 15 cases it ranged between 110 and 150 mg. This fraction represents 23 to 40 per cent of the total nitrogen after hydrolysis, with an average of 28 per cent. The lowest mono-amino nitrogen value was 190 mg., the highest 330 mg., and the average 269 mg. It

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TABLE I

Nitrogen Distribution of the Serum Proteins in Normal Adults

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen * after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm. Hg	mg. per 100 c.c.				mg. per 100 c.c.			
115	26	130/80	570	510	120	23	380	220	43	1.8
116	24	120/80	700	680	190	28	490	310	46	1.6
117	28	118/70	600	550	150	27	390	330	60	2.2
118	24	105/70	600	570	130	23	430	260	45	2.0
119	28	135/85	630	600	180	30	420	230	38	1.3
120	26	118/70	530	450	130	29	310	310	69	2.3
121	25	115/80	530	480	150	31	320	300	62	2.0
122	32	114/70	600	580	190	33	390	310	53	1.6
123	29	104/70	560	470	190	40	280	190	40	1.0
3	28	130/78	530	510	130	25	370	250	48	1.9
4	21	106/76	480	470	130	27	320	240	51	1.8
8	27	120/70	550	540	140	26	400	300	55	2.1
10	27	116/63	520	500	140	28	360	280	56	2.0
18	25	106/50	510	490	130	27	360	290	59	2.2
27	28	120/80	470	450	130	29	320	280	62	2.1
28	31	112/80	500	480	120	25	360	280	58	2.3
79	25	130/95	450	430	130	30	390	280	65	2.1
80	24	118/90	420	400	100	25	300	220	55	2.2
81	28	126/80	460	430	110	25	320	250	58	2.2
83	25	110/82	430	400	120	30	270	260	65	2.1
High	32	S135 D95	700	680	190	40	490	330	69	2.3
Low	21	S104 D50	420	400	100	23	270	190	40	1.0
Average	26	S117 D76	532	499	140	28	359	269	54	1.9

Pulse Pressure: High 56; Low 28; Average 41.
* After the removal of humin and amide nitrogen.
The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen.

was between 200 and 300 mg. in 13 cases (65 per cent) and in 6 cases (30 per cent) between 300 and 330. The mono-amino nitrogen expressed as percentage of the total nitrogen after hydrolysis varied between 40 and 69, with an average of 54. The M/B ratio varied between 1.0 and 2.3, with an average of 1.9. The ratio in one case was 1.0, in 6 cases (30 per cent) between 1.1 and 1.9, and in 13 cases (65 per cent) between 2.0 and 2.3.

Control Cases without Hypertension. Table 2 records the nitrogen distribution in 11 individuals who, while not normal, suffered from conditions in which hypertension was not a factor; four were cases of cardiac disease, three of diabetes and one each of tetany, carcinoma of the rectum, and hemiplegia. The ages of this group varied between 29 and 81 years and the blood pressure between 105 systolic and 70 diastolic and 140 systolic and 70 diastolic. The basic amino nitrogen was slightly lower, while the mono-amino nitrogen values approximated those of the normal group. The

TABLE II

Nitrogen Distribution of Serum Proteins in Miscellaneous Disease Conditions without Hypertension

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm. Hg	mg. per 100 c.c.				mg. per 100 c.c.			
9	61	130/90	430	400	100	25	300	290	72	2.9 Myocarditis
44	74	140/70	500	480	120	25	360	290	60	2.4 "
113	38	112/74	580	500	100	20	400	320	64	3.2 "
15	50	140/90	530	510	120	23	390	290	57	2.4 Sinus arrhythmia
64	71	120/70	530	520	120	23	400	300	57	2.5 Diabetes
76	71	130/80	430	390	100	25	290	250	64	2.5 "
78	80	130/80	400	370	100	27	270	260	70	2.6 "
109	34	120/70	640	600	130	21	470	240	40	1.8 "
32	29	105/70	500	470	100	20	370	220	47	2.2 Tetany
62	81	140/70	420	380	100	26	280	250	66	2.5 Hemiplegia
112	64	130/90	620	470	120	25	350	320	70	2.6 Ca. of rectum
High		S 140 D 90			130	27		320	72	3.2
Low		S 105 D 70			100	20		220	40	1.8
Average		S 127 D 77			110	23		275	60	2.5

Pulse Pressure: High 70; Low 35; Average 50.
* After the removal of humin and amide nitrogen.
The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen.

M/B ratio was slightly higher than normal, being in 10 cases (91 per cent) between 1.0 and 2.9.

NITROGEN DISTRIBUTION IN HYPERTENSION

In experimental hypertension, as previously stated, the changes in the nitrogen distribution of the serum proteins are in (*a*) the basic amino nitrogen, (*b*) the mono-amino nitrogen, or (*c*) in both. In hypertension in man similar changes have been found and the cases grouped accordingly.

Group A: Hypertension with a lowered basic amino nitrogen, an increased mono-amino nitrogen, and an increased M/B ratio.

The data in a series of 18 cases showing a change in both nitrogen fractions are given in table 3. The ages of the individuals varied between 24 and 77 years, with an average of 56. The range of the systolic blood pressure varied between 165 and 286, with an average of 208; and the diastolic pressure varied from 70 to 142, with an average of 101. The pulse pressure varied between 65 and 200, with an average of 106.

The basic amino nitrogen varied between 60 and 90 mg. with an average of 75 mg. and formed between 10 and 21 per cent with an average of 15 per cent of the total nitrogen after hydrolysis. The mono-amino nitrogen ranged between 330 and 590 mg. with an average of 462 mg. This fraction forms between 73 and 100 per cent with an average of 83 per cent of the total nitrogen after hydrolysis. The M/B ratio was the highest obtained of all the cases of hypertension studied, varying between 3.6 and 9.8 with an

average of 5.7. A comparison of the data obtained in this group with that of the normals shows a definite alteration in the nitrogen distribution.

One exception was encountered. Case 55, a male aged 42 years, with blood pressure of 128 systolic and 60 diastolic, whose nitrogen distribution was similar to that observed in the cases of hypertension. This individual had a neurosis and was considerably overweight. The urine was negative and there was no evidence of nitrogen retention in the blood. The blood

TABLE III

Nitrogen Distribution of Serum Proteins in Hypertension. Cases Showing Decreased Basic Amino Nitrogen and Increased Mono-Amino Nitrogen and M/B Ratio

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm. Hg	mg. per 100 c.c.				mg. per 100 c.c.			
30	49	165/90	500	440	90	20	350	350	80	3.9
84	52	170/95	730	480	80	17	370	360	75	4.5
85	44	208/118	666	580	60	10	600	590	100	9.8
89	67	190/110	550	490	70	14	420	420	86	6.0
91	64	210/105	800	600	70	12	550	550	90	7.8
92	62	185/120	660	640	80	12	580	490	76	6.1
93	49	210/100	590	560	60	11	500	500	89	8.3
94	61	190/80	650	500	70	14	430	430	86	6.1
95	36	200/100	620	520	70	13	450	420	80	6.0
96	42	220/140	530	500	80	16	420	410	82	5.1
97	24	170/70	570	500	80	16	420	420	84	5.2
98	74	236/84	640	610	70	11	540	500	82	7.1
99	55	286/86	560	500	80	16	420	420	80	5.2
87	41	224/142	710	460	70	17	390	390	84	5.5
60	77	220/90	500	480	80	17	400	400	83	5.0
34	70	230/100	450	420	90	21	330	330	80	3.6
36	68	205/100	450	430	80	18	350	330	76	4.1
61	74	200/100	520	490	80	16	410	360	73	4.5
High		S 286 D 142			90	21		590	100	9.8
Low		S 165 D 70			60	10		330	73	3.6
Average		S 208 D 101			75	15		426	83	5.7
Nonhypertensive										
55	43	128/60	500	450	80	18	370	360	80	4.5 Neurosis, Hyperthyroid

Pulse Pressure for hypertensive cases: High 200; Low 65; Average 106.
* After the removal of humin and amide nitrogen.
The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen.

serum cholesterol was 145 mg. per 100 c.c. and the basal metabolic rate was plus 14 per cent. There was no previous history of hypertension.

Group B: Hypertension with a decrease in the basic amino nitrogen and no changes in the mono-amino nitrogen.

The data of the examinations in the 14 cases comprising this group are given in table 4. The age of the patients varied between 22 and 83 with an average of 62 years. The systolic blood pressure varied between 150 and 230 with an average of 180, while the diastolic pressure varied between 80 and 120 with an average of 100. The pulse pressure range was between 50

and 120 with an average of 81. The basic amino nitrogen values varied between 70 and 90, with an average of 84 mg.; thus, this fraction varied between 13 per cent and 25 per cent with an average of 19 per cent of the total nitrogen after hydrolysis. The values for the basic amino nitrogen and the percentage of the total nitrogen after hydrolysis were slightly higher than those in group A.

While the mono-amino nitrogen values were within normal limits, the per cent this fraction formed of the total nitrogen after hydrolysis is lower

TABLE IV

Nitrogen Distribution of Serum Proteins in Hypertension. Cases Showing a Decreased Basic Amino Nitrogen

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen * after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm. Hg	mg. per 100 c.c.				mg. per 100 c.c.			
37	73	230/120	430	410	90	22	320	300	73	3.3
38	70	190/105	520	500	90	18	410	270	54	3.0
45	73	150/95	500	480	90	19	390	310	64	3.4
46	72	150/90	550	520	70	13	450	310	60	4.4
47	30	145/90	490	470	90	19	380	310	66	3.4
65	60	195/100	400	370	70	18	300	300	81	4.3
66	22	150/95	440	410	90	22	320	290	70	3.2
68	72	210/110	420	390	80	20	310	300	77	3.7
69	82	210/90	470	450	70	15	380	270	60	3.8
71	67	198/90	400	370	90	24	280	280	75	3.1
72	70	150/80	440	410	90	22	320	290	70	3.2
74	70	160/90	400	360	90	25	270	270	75	3.0
70	72	190/100	500	470	80	19	390	220	46	2.7
108	56	178/120	550	470	90	19	380	220	47	2.4
High	82	S230 D120			90	25		310	81	4.4
Low	22	S150 D 80			70	13		220	46	2.4
Average	62	S180 D100			84	19		281	65	3.4

Pulse Pressure: High 120; Low 50; Average 81.
* After the removal of humin and amide nitrogen.
The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen.

than those of group A, but higher than the normal group. The actual values varied between 220 and 310 mg. with an average of 281 mg. The M/B ratio varied between 2.4 and 4.4 with an average of 3.4. These values, while not as high as those in group A, are increased over the normal.

Group C: Hypertension in which there is an increase in the mono-amino nitrogen fraction only.

The largest number of our hypertensive cases are those in which there was a rise in the mono-amino nitrogen only. The data of these cases are

given in table 5. The group comprises 32 cases, the ages ranging between 26 and 87 with an average of 56 years. The systolic blood pressure varied

TABLE V

Nitrogen Distribution of Serum Proteins in Hypertension. Cases Showing Increased Mono-Amino Nitrogen

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio	
		mm. Hg	mg. per 100 c.c.				mg. per 100 c.c.				
2	50	164/100	650	630	120	20	510	500	79	4.1	
7	67	180/102	560	540	100	18	440	430	80	4.3	
14	51	195/110	630	620	110	17	510	500	80	4.5	
17	42	235/140	550	530	120	22	410	400	75	3.3	
19	46	205/118	750	730	130	17	600	580	80	4.4	
20	39	152/80	530	520	120	23	400	360	70	3.0	
22	26	155/85	560	540	120	22	420	400	74	3.3	
23	79	155/82	650	630	120	19	510	500	80	4.1	
31	69	170/90	540	500	100	20	400	360	72	3.6	
33	69	210/100	550	530	120	22	410	380	71	3.1	
39	87	235/120	500	480	110	23	370	330	70	3.0	
42	71	195/70	600	570	140	24	430	430	75	3.0	
43	69	200/100	600	570	120	21	450	450	80	3.7	
49	65	210/115	530	500	110	22	390	400	80	3.6	
51	79	230/115	540	520	100	19	420	400	77	4.0	
54	78	195/75	500	480	110	23	360	360	75	3.2	
75	31	250/160	520	480	110	23	360	340	71	3.1	
86	27	156/92	600	440	100	22	340	330	75	3.3	
88	38	182/116	950	710	110	15	580	580	81	5.2	
90	60	210/105	1020	850	110	13	740	750	88	6.8	
100	54	180/80	500	480	120	25	360	360	75	3.0	
101	40	194/108	750	700	130	19	570	570	81	4.3	
102	64	215/120	990	770	148	19	620	620	80	4.1	
103	47	160/50	600	580	130	22	460	510	88	3.9	
6	49	156/94	510	490	110	22	370	360	73	2.2	
107	53	234/156	660	590	180	30	400	420	71	2.3	
104	42	188/116	650	610	190	31	420	390	64	2.0	
105	52	210/110	550	490	150	30	340	340	70	2.2	
67	73	200/110	520	500	160	32	340	330	66	2.0	
52	74	172/82	600	560	130	23	430	360	64	2.7	
11	45	156/100	520	500	120	24	380	350	80	2.9	
48	74	230/120	540	510	100	19	410	330	64	3.3	
High	87	S 250 D 160			190	32		750	88	6.8	
Low	26	S 152 D 50			100	13		330	64	2.0	
Average	56	S 193 D 103			123	22		428	75	3.5	

Pulse Pressure: High 120; Low 56; Average 89.

Nonhypertensive

12	17	106/61	550	530	160	30	370	360	68	2.1	Splenectomy
13	20	106/66	540	520	120	23	400	360	69	3.0	"
29	55	100/60	550	530	110	20	420	400	75	3.6	"
16	56	118/60	500	480	100	20	380	360	75	3.6	Per. anemia
21	55	108/58	560	540	120	20	420	400	74	3.3	Absc. of liver
26	33	115/78	650	640	120	19	520	510	80	4.2	Acute uremia Hodgkin's dis.
24	64	110/90	540	520	120	23	400	390	75	3.2	Scl. of aorta Hyper. prostate

* After the removal of humin and amide nitrogen.
The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen.

between 152 and 250 with an average of 193, and the diastolic pressure varied between 50 and 160 with an average of 103. The pulse pressure ranged between 56 and 120 with an average of 89. The basic amino nitro-

gen varied between 100 and 190 with an average of 123 mg. and formed from 13 per cent to 32 per cent with an average of 22 per cent of the total nitrogen after hydrolysis. The mono-amino nitrogen fraction varied between 330 and 750 mg. with an average of 428 mg., as compared with an average of 269 mg. for the normal group. This fraction represents between 64 per cent and 88 per cent of the total nitrogen after hydrolysis with an average of 75 per cent as compared with an average of 54 per cent obtained for the normal group. The M/B ratio varied between 2.0 and 6.8 with an average of 3.5 as compared with an average of 1.9 for the normal group.

Exceptions: There were seven individuals with normal blood pressure whose nitrogen distribution showed an increase in the mono-amino nitrogen fraction. Among these were three cases from which the spleen had been removed, and one each of pernicious anemia, abscess of the liver complicated with acute uremia, hypertrophied prostate, and Hodgkin's disease. The mono-amino nitrogen values of these nonhypertensive cases varied between 360 and 510 mg. with an average of 354 mg. The M/B ratio varied between 2.1 and 4.2 with an average of 3.1.

Group D: Hypertension with normal nitrogen distribution.

In table 6 are given the data on 12 cases of hypertension in which there were no significant changes from the normal in the nitrogen distribution of

TABLE VI

Cases of Hypertension Showing Normal Nitrogen Distribution

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio	
		mm. Hg	mg. per 100 c.c.				mg. per 100 c.c.				
25	34	185/138	450	430	110	25	300	300	70	2.7	Arteriosclerosis. Obesity
35	70	190/85	590	560	100	18	460	250	44	2.5	Arteriosclerosis
41	69	225/90	500	480	100	20	380	290	60	2.9	Arteriosclerosis. Myocarditis
53	67	205/110	520	490	100	20	390	320	65	3.2	Arteriosclerosis
57	71	230/100	500	370	100	27	270	240	67	2.4	Arteriosclerosis. Obesity
58	80	200/70	520	490	110	22	380	300	61	2.7	Arteriosclerosis. Myocarditis
106	49	252/140	570	490	150	30	330	310	63	2.0	Uremia
110	16	138/90	560	500	160	32	340	250	50	1.5	Chr. tonsillitis
63	73	170/70	470	450	120	26	330	230	51	1.9	Arteriosclerosis. Diabetes
73	68	220/190	470	440	100	22	330	290	66	2.9	Arteriosclerosis
50	75	160/70	570	550	120	22	430	300	54	2.5	Arteriosclerosis. Diabetes
56	6	117/82	440	420	110	25	310	250	60	2.2	Acute hem. nephritis
High		S 252 D 190			160	32		320	70	3.2	
Low		S 117 D 70			100	18		230	44	1.5	
Average		S 191 D 94			115	24		277	59	2.4	

Pulse Pressure: High 135; Low 35; Average 96.

* After the removal of humin and amide nitrogen.

The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen.

the serum proteins. The systolic blood pressure of this group varied between 117 and 252 with an average of 191, the diastolic pressure between 70 and 190 the average being 94, while the pulse pressure varied between 35 and 135 with an average of 96.

Discussion

In 84 per cent of the cases of hypertension which we have studied there were definite changes in the nitrogen distribution of the serum proteins. When either the basic amino or mono-amino nitrogen fractions were altered, the degree of hypertension was about the same as determined by the averaged systolic and pulse pressures. These averaged pressures, however, were higher when both nitrogen fractions were involved in the change. This suggests some correlation between the degree of hypertension and the nitrogen distribution, although the exact relationship cannot be stated at the present time. From the results of animal experimentation,[1] hypertension seems to precede changes in the M/B ratio.

Although the majority of the cases of hypertension showed a change in the nitrogen distribution, there were 12 cases in which no change was demonstrable. In most of these exceptions the dominant clinical complaint was that of atherosclerosis rather than hypertension. In other hypertensive individuals in whom alterations in the M/B ratio was observed, atherosclerosis was not the dominant clinical complaint.

In previous work [1] an extensive fibrosis of the spleen was noted in animals suffering from aspartic acid induced hypertension, and it was pointed out that fibrotic changes also occurred in the spleen of human cases suffering during life with hypertension. It is interesting to note in the light of these observations that in five of the seven nonhypertensive cases exhibiting an altered nitrogen distribution, disturbances in the reticulo-endothelial system were evident. In three of these cases the capacity of the reticulo-endothelial system was greatly reduced by removal of the spleen; another suffered from pernicious anemia, a condition in which the spleen shows marked fibrotic changes; and the fifth from Hodgkin's disease which broadly considered is a lesion of the reticulo-endothelial system. These changes which occurred in (*a*) the spleens of hypertensive animals, (*b*) the spleens of human cases dying of hypertension and (*c*) in the reticulo-endothelial system of nonhypertensive cases suggests that the reticulo-endothelial system or the spleen plays a rôle in maintaining the M/B ratio at a normal level.

In the cases of hypertension with a low basic amino nitrogen, there was little or no evidence of nephritis. A review of the clinical aspects of the cases of hypertension having increased mono-amino nitrogen showed in the greater majority of the patients a mild degree of nephritis without retention of the non-protein nitrogenous constituents. Four of the cases, however, showed slight nitrogen retention. In the group of hypertensive cases in which both nitrogenous fractions deviated from the normal, there was us-

ually evidence of a marked nephritis with nitrogen retention in the blood to a varying degree.

On the basis of the chemical and clinical studies in the group of hypertensive cases reported in this paper, the following classifications appear possible:

Class 1. Hypertensive individuals whose blood serum proteins showed a decreased basic amino nitrogen and an increased mono-amino nitrogen. This group showed evidence of a severe nephritis with moderate non-protein nitrogen retention in the blood which occasionally was severe.

Class 2. Cases of hypertension in which the blood serum proteins showed a low basic amino nitrogen, no change in the mono-amino nitrogen fraction and little or no evidence of nephritis.

Class 3. Cases of hypertension in which only the mono-amino nitrogen fraction of the blood serum proteins was increased. This group showed a moderate nephritis, occasional nitrogen retention, with little or no evidence of arteriosclerosis.

Class 4. Cases of hypertension in which the basic amino and mono-amino nitrogen fractions were within normal limits. These cases showed arteriosclerotic changes and symptoms. This group did or did not have evidence of kidney impairment.

On the basis of the classifications outlined above, one might readily speculate both as to the etiology of hypertension and as to therapeutic possibilities. It might be that the changes noted in the nitrogen distribution are due to a functional disturbance of the reticulo-endothelial system. Organotherapy of the reticulo-endothelial system might prove to be of therapeutic benefit alone, or in combination with dietary changes. It is possible that the hypertension might disappear if the ratio between these two nitrogen fractions could be restored to normal by raising the basic amino nitrogen. In the animal experiments as reported elsewhere,[1] the mono-amino nitrogen values dropped when the injections of aspartic acid were discontinued and the blood pressure returned to normal. It is within the realm of possibility to raise the basic amino nitrogen values by suitable changes in the diet.

Conclusions

1. Changes from the normal were observed in 84 per cent of 76 cases of hypertension in either the basic amino or mono-amino nitrogen fractions of the blood serum proteins or in both these fractions; the change in 23 per cent was in both fractions; in 18 per cent only the basic amino nitrogen was altered; in 42 per cent the mono-amino nitrogen alone was changed and in 15 per cent no change in either fraction was demonstrable.

2. Based upon these chemical changes, a classification of cases of hypertension is proposed. The more exact details of the various groups are given in the body of the paper.

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SEDIMENTATION TIME IN ACUTE CARDIAC INFARCTION *

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In 1931 the authors reported 10 cases of acute cardiac infarction secondary to coronary artery thrombosis in which the red blood cell sedimentation time was studied.[1] Burak [2] subsequently reported a similar study, but the literature on the subject has, in general, been scant. Singer [3] and Wollheim [4] have both mentioned the increased rapidity of red cell sedimentation rate as a diagnostic factor in coronary thrombosis. Because the sedimentation time has frequently been of great help to us in the diagnosis and treatment of acute coronary thrombosis, we are reporting an additional series of cases studied during the past three years.

Method

The sedimentation times were done according to the method of Linzenmeier.[5] Sixty minutes has been taken as the lower limit of normal, i.e. sedimentation more rapid than 60 minutes to the 18 mm. mark is regarded as abnormal. No corrections were made for variations in the red blood cell count, but this did not appear to make a serious difference in this series.

Twenty-nine cases of acute coronary thrombosis were studied. In all cases included in this series, the clinical diagnosis was confirmed by electrocardiography. Of nine patients who died, five were autopsied, and an acute coronary thrombosis found. Cases which had complicating disease which might influence the sedimentation rate were excluded.

Results

In *all* the cases studied the sedimentation time was abnormally rapid at some time during the course of the disease. In all the cases but one, the rate was abnormally rapid by the fifth day. In the one exception the figure did not go below 60 minutes until the second week, but even in this case a drop was apparent toward the end of the first week. (Chart 1.) In several cases the sedimentation time became abnormal as early as the second day. (Chart 2.) The earliest in this series at which the sedimentation time returned to normal was the thirteenth day, and the latest, the thirty-ninth day. At times it was kept rapid over a rather long period by repeated thromboses. (Charts 2 and 3.)

In two cases the temperature and leukocyte count were normal throughout while the sedimentation time was definitely abnormal. In most of the

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CHART I
A. S., Male, Aged 42 Years

Day of Illness	Date	Maximum Temp.	Maximum Pulse	White Blood Count	Polys.	Sedimentation Time to 18 mm.
2	4–29–31	99.2	84			270 minutes
3	4–30–31	99.4	108	16,800		
4	5– 1–31	99.8	128			135 minutes
5	5– 2–31	100.4	116			
6	5– 3–31	99.8	104	15,800	66%	65 minutes
7	5– 4–31	99.4	104			
8	5– 5–31	99.2	96	11,100	55%	60 minutes
9	5– 6–31	99.6	80			
10	5– 7–31	99.4	78			
11	5– 8–31	99.6	78	10,700	63%	49 minutes
12	5– 9–31	99.6	82			
13	5–10–31	99.6	84			
14	5–11–31	99.2	86	10,100	51%	55 minutes
15	5–12–31	98.8	84			
16	5–13–31	98.8	80			
17	5–14–31	98.8	84	9,850	51%	60 minutes
18	5–15–31	99.2	86			
19	5–16–31	98.8	76			
20	5–17–31	99.2	80			
21	5–18–31	99.0	82	8,500	58%	90 minutes

Remarks: Closure on April 28, 1931.
Hemoglobin 90%.
R. B. C., 4,700,000.
Electrocardiograms: Inversion of T-wave in all leads. Later T-wave became positive, and a left axis deviation developed.

CHART II
S. H., Male, Aged 54 Years

Day of Illness	Date	Maximum Temp.	Maximum Pulse	White Blood Count	Polys.	Sedimentation Time to 18 mm.
3	11–12–32	99.4	102	7,400	69%	55 minutes
13	11–22–32	99.0	90			37 minutes
17	11–26–32	98.6	84			30 minutes

Remarks: First closure on November 8, 1932.
Hemoglobin 80%.
R. B. C., 4,250,000.

2	6–28–33	98.2	100			40 minutes
3	6–29–33	99.6	106	18,600	75%	
8	7– 6–33	99.4	96	18,000	67%	
15	7–13–33	104.0	104			43 minutes
22	7–20–33	99.4	104			60 minutes
28	7–26–33	98.6	96	7,800	68%	45 minutes
37	8– 4–33	99.0	90			52 minutes
42	8– 9–33	98.6	90			50 minutes
49	8–16–33	98.6	96			85 minutes

Remarks: Second closure on June 26, 1933.
Hemoglobin 85%.
R. B. C., 3,350,000.
Electrocardiograms: November 19, 1932: Left axis deviation. Q-R-S slurred. S-T isoelectric. T_1 sharply inverted; T_2 and T_3 upright.
June 28, 1933: Definite Q_3-T_3 type. S-T_2 and S-T_3 markedly elevated; S-T_1 depressed. T_1 upright; T_2 and T_3 sharply inverted.

CHART III

L. G., Female, Aged 61 Years

Day of Illness	Date	Maximum Temp.	Maximum Pulse	White Blood Count	Polys.	Sedimentation Time to 18 mm.
2	10–14–32	102.0	140	11,800	79%	
3	10–15–32	101.6	110			
4	10–16–32	101.0	92			29 minutes
12	10–24–32	100.4	92	9,600	74%	
15	10–27–32	100.2	90			23 minutes
20	11– 1–32	99.4	96	9,600	66%	
23	11– 4–32	99.0	94			21 minutes
27	11– 8–32	100.2	90			21 minutes

Remarks: Multiple thromboses; first one on October 13, 1932.
Hemoglobin 65%.
R. B. C., 3,600,000.

Electrocardiograms: October 18, 1932: Left axis deviation. Occasional ventricular extrasystoles. Marked slurring of the Q-R-S.
Repeated on November 1 and 15 without any essential change.

cases there were fever and leukocytosis during the first few days at which time the sedimentation rate was normal. Toward the end of the first week the temperature and leukocyte count returned to normal while the sedimentation rate became definitely abnormal. The sedimentation rate then continued rapid for several weeks while the temperature and leukocyte count remained normal. Typical cases are illustrated in charts 4 and 5.

CHART IV

H. S., Male, Aged 48 Years

Day of Illness	Date	Maximum Temp.	Maximum Pulse	White Blood Count	Polys.	Sedimentation Time to 18 mm.
7 days prior to closure	10–10–33	98.6	92	8,000	71%	More than 120 minutes
2	10–18–33	102.4	120	17,200	88%	
4	10–20–33	101.0	110			
7	10–24–33	98.6	82			15 minutes
10	10–27–33	98.6	90	9,500	61%	
14	10–31–33	100.0	110			45 minutes
20	11– 6–33	99.0	80			85 minutes
22	11– 8–33	98.6	80			More than 120 minutes

Remarks: Admitted because of severe angina of effort.
Closure in hospital on October 17, 1933.
Hemoglobin 86%.
R. B. C., 4,600,000.

Electrocardiograms: October 10, 1933: Slurring of Q-R-S. S-T is isoelectric. T_1, T_2 upright; T_3 inverted.
October 20, 1933: R-T segment in Leads I and II markedly elevated, arising from the downstroke of "R".
November 1, 1933: R-T is isoelectric. T_1 sharply inverted; T_2 and T_3 are upright.

CHART V

J. M., Male, Aged 47 Years

Day of Illness	Date	Maximum Temp.	Maximum Pulse	White Blood Count	Polys.	Sedimentation Time to 18 mm.
3	9– 6–32	101.4	108			
4	9– 7–32	101.6	112	24,000	78%	120 minutes
5	9– 8–32	100.8	100			
6	9– 9–32	100.8	92			19 minutes
7	9–10–32	100.2	86			
8	9–11–32	100.4	88			
9	9–12–32	100.0	86			
10	9–13–32	99.0	96	8,000	64%	
11	9–14–32	99.0	88			
12	9–15–32	99.0	90			20 minutes
24	9–27–32	100.0	80	8,400	72%	160 minutes
29	10– 2–32	100.0	80			170 minutes

Remarks: Closure on September 4, 1932.
Hemoglobin 100%.
R. B. C., 6,510,000 (Emphysema probable cause of slight polycythemia).

Electrocardiograms: September 10, 1932: Q-R-S slurred. R-T_1 and R-T_2 markedly elevated. T-wave is upright.
September 28, 1932: T_1 and T_2 sharply inverted; T_3 upright. R-T_1, R-T_2 and R-T_3 isoelectric and somewhat rounded.
October 4, 1932: As before, except for inversion of T_3 as well as of T_1 and T_2.

DISCUSSION

Patients not infrequently present themselves with a history of an attack of angina pectoris occurring several days or even several weeks previously which arouses suspicion of a recent coronary artery thrombosis. The temperature and blood count are usually normal at this time, and the electrocardiogram may frequently be indefinite. It is in these cases that we have found the sedimentation time to be of great help, and where an electrocardiograph is not available, the increased sedimentation rate may be the only definite evidence of active cardiac muscle involvement.

Even where the diagnosis is clear, we believe it is of definite value to follow the sedimentation time. We have found it to be a sensitive indicator of subsequent thrombosis in the heart or elsewhere, or of embolus or infection. (Chart 5.) It enables one, too, to estimate the rapidity of healing. At the present time there is no definite evidence that the rapidity of the sedimentation time is proportionate to the extent of the damage in the heart, but it seems justifiable to assume that while the determination is abnormal, active changes are taking place in the heart muscle. We believe that the sedimentation time makes less arbitrary the duration of bed rest for a particular case and that a patient with an acute coronary closure should be kept in bed at least until this determination has returned to normal. We wish to emphasize the importance of a careful search for infection or infarction outside the heart before a cardiac significance is attached to a rapid sedimentation rate.

Conclusions

1. The red blood cell sedimentation time was studied in 29 cases of acute cardiac infarction. It was abnormally rapid in all.

2. It became rapid between the second and fifth days and returned to normal between the thirteenth and thirty-ninth days.

3. An abnormal sedimentation rate may outlast the return of temperature and leukocyte count to normal by as much as four weeks. It may be abnormal when the temperature and leukocyte count have been normal throughout.

4. It is of great help in cases seen first several days or weeks after the occurrence of a cardiac infarction.

5. It helps in the recognition of subsequent thrombosis or infection.

6. It makes less arbitrary the duration of bed rest.

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COMBINED MEDICAL AND SURGICAL MANAGEMENT OF PEPTIC ULCER; WITH EMPHASIS ON THE TREATMENT OF HEMORRHAGE *

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THE first pre-requisite for an intelligent approach to the treatment of peptic ulcer by any method is an accurate conception of the pathologic changes in the gastroduodenal mucous membrane which are designated as "peptic ulcer." This term has been applied to all variations of pathologic changes from a simple erosion of the mucosa to a deep penetrating lesion with attachments to the neighboring viscera. The confusion that exists in the general medical mind relative to peptic ulcer can be directly attributed to the fact that frequently the disputants have entirely different lesions in mind. Then strangely enough the disease seems to vary in different races both in incidence and severity. The Hebrew evidently is more prone to peptic ulcer and its complications than is the Aryan. Walters and Snell,[1] who are quite familiar with the clinical and surgical manifestations of ulcer in the United States, observed that the central European nations present a different anatomico-pathologic picture from that seen in this country. The Austrian peoples are more prone to multiple ulcerations combined with a severe chronic gastritis, whereas the lesion most often seen in America is a single localized area of inflammatory change with the remainder of the mucosa in an approximately normal state. The important point then in any discussion of peptic ulcer is to so focus the attention that everyone has the identical pathologic process in mind.

The experience of the authors has been chiefly comprised of patients from the middle western United States, most of whom have been of northern European origin but including a liberal number of Semitic descent. Peptic ulcer in these peoples is usually confined in number to a single lesion and is more frequently situated in the duodenum than in the stomach. It has been our observation that multiple ulceration when it occurs is more common in the duodenum.

Therefore, for the purposes of this paper we will define peptic ulcer as solution in the continuity of the gastroduodenal mucosa, varying between lesions of minute size and confined superficially to the mucosa, and the larger, punched out, characteristic ulceration with a definite crater and a base that is comprised of scar tissue of variable extent. These lesions may be multiple, especially in the duodenum, and have a distinct tendency to heal and recur periodically with an increasing deposit of cicatrix after each episode. As the process advances, perforation through the walls of the stomach

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From the Soper-Mills Clinic.

or duodenum may take place, at times quite rapidly and in other instances over prolonged periods of time. During this process attachment to neighboring viscera or even perforation into them may occur.

The etiology of peptic ulcer still remains unproved. The experimental surgeons have presented evidence that ulcer is due to acid gastric secretions acting on the mucous membrane that lacks some neutralizing factor to adjust the fine physiologic balance between the secretions and enzymes of the digestive juices of the stomach, duodenum, pancreas and liver. Mann and Williamson [2] have produced experimentally so-called surgical duodenal drainage peptic ulcers in dogs that are indistinguishable histologically from those found in humans. Quite recently Bollman and Mann,[3] corroborating the experiments of Von Wagoner and Churchill,[4] have described ulcers produced in dogs by prolonged ingestion of the drug cinchophen. These ulcerations are likewise quite similar to those seen clinically.

The healing process in ulcer of the stomach and duodenum is an exact counterpart of that observed in varicose ulcer of the leg. The crater of the ulcer is gradually filled in with fibrin, and the epithelial edges proliferate toward the center, gradually closing the defect. Just as the varicose ulcer of the lower leg needs to be protected from traumatization of the delicate, tender, fragile, advancing margin of newly forming epithelium, so does the ulcer of the gastroduodenal mucosa need to be guarded. The slightest trauma will dislodge the plug of fibrin in the base of the crater, disrupting the newly forming glandular epithelium and leaving the base vulnerable to the acid gastric secretions. These points were admirably demonstrated in the experimental work of Mann [5] presented at a recent Hodgen lecture. The practical clinical application is obvious.

Malignant degeneration of peptic ulcer of the gastric mucosa is a distinct possibility. It practically never happens in the duodenal lesion. McCarty [6] long ago advanced the theory of metaplasia from peptic ulcer to gastric cancer. Therefore, ulcer of the stomach must be classified as benign or malignant. Alvarez [7] has stated that any gastric ulcer larger than a dime is potentially malignant, and gastric resection should be seriously considered in such patients no matter what the age may be.

The association of gastric and duodenal ulcer in the same patient is of frequent occurrence, and the possibility of a carcinoma of the stomach should always be kept seriously in mind in any case of duodenal ulcer presenting a persistent occult blood reaction in the feces. It is quite possible that there may be roentgen-ray evidence of deformity in the duodenal cap or in the region of the pylorus, and that a severe hemorrhage from a gastric cancer may be mistakenly attributed to the old ulcer in the duodenum. The following case history strikingly illustrates this point.

Mrs. Ursula M., aged 45, a married woman, presented herself at the clinic complaining of dyspepsia and belching accompanied by a burning sensation in the epigastric region. General physical examination revealed that she was of the asthenic type with visceroptosis. Examination of the feces by the guaiac test showed occult

blood present persistently despite adequate medical treatment. The patient was advised to have surgical exploration because of this but refused to consider it. In addition there was a filling defect of a seemingly benign nature at the pyloric ring. No evidence of filling defect in the stomach was observed. While under observa-

FIG. 1. Roentgenogram demonstrating atonic stomach with duodenal ulcer. (Note smoothness of outline of both greater and lesser curvature.)

tion, and having refused elective operation, she was taken with a severe series of hemorrhages which depleted her circulation of blood until her erythrocyte count was approximately 1,200,000 and her hemoglobin 25 per cent (Dare). She was im-

mediately hospitalized and given three blood transfusions, while under the trans-nasal suction siphonage method of treatment for hematemesis. As soon as her condition permitted she was operated upon and the source of the bleeding was found to be not in the pyloric region as suspected (figure 1) but arising from the base of a shallow

FIG. 2. Postoperative roentgenogram of same patient as in figure 1 following partial gastrectomy with removal of segment of stomach containing grade III carcinoma.

gastric cancer situated on the greater curvature of the stomach. A partial gastrectomy was done removing approximately two-thirds of the stomach well above the growth. The patient made a good recovery and examination of the stools has been

negative. Roentgen-ray films show the remaining portion of the stomach smooth in outline with no evidence of recurrence (figure 2).

This case is presented to demonstrate the association of gastric cancer with duodenal and prepyloric benign lesions. The roentgen-ray here did not disclose the lesion situated on the greater curvature of a large visceroptotic stomach. It is well to reiterate that a persistent occult blood reaction (guaiac) in the feces when the patient is on a meatless dietary regimen should always excite the suspicion of malignancy. Surgical exploration should be advised even in the absence of a lesion demonstrable by means of the roentgen-ray.

In complicated gastroduodenal ulcer the combination of a medically minded surgeon with a clinician who fully appreciates the advantages of surgery offers the patient the greatest chance of permanent relief. In the type of individual who has what we may term "ulcer diathesis" neither medical nor surgical treatment offers very promising results. These are the patients who have recurrent ulcerations after any and all types of surgery, gastric resection not excluded. The simple benign uncomplicated peptic ulcer of the gastroduodenal mucosa is the type amenable to successful treatment by a medical regimen of which there are innumerable variations.

Medical management of duodenal ulcer has been greatly simplified in recent years and placed on a more rational basis. There has been some tendency to make it difficult again by employing various hypodermic injections of organic compounds of histidine. Most of these methods are accompanied by careful dietetic instructions and it is of extreme uncertainty where to attribute the credit for any relief obtained. All tissues, more especially epithelial structures throughout the body, have an inherent biologic tendency to proliferate and heal over any break in their continuity. Hargis and Robertson [8] demonstrated by postmortem studies on patients who succumbed to unrelated constitutional diseases that evidences of old healed scars of peptic ulcers were present when no mention had been made of gastric symptoms in the patients' chief complaints. Upon interrogation of the near relatives of these deceased patients it was learned that they did have "stomach trouble" (symptoms of peptic ulcer) for which they quite frequently never consulted a physician. Consequently, it is quite justifiable to conclude that there are many individuals who have mild peptic ulcers which undergo several periods of recurrence without causing severe symptoms.

The smooth diet, judiciously increased according to the progress of the patient's symptoms and combined with sedative drugs and alkalies to diminish hyperacidity, forms the orthodox rationalized basis of treatment founded on an accurate understanding of the fundamental pathologic processes involved and the physiologic resources of the patient required to promote healing of the lesions. In the acute stages a diet consisting chiefly of milk and cream, junket, thin cooked cereals, with cream and sugar added, forms the standard measure employed. The feedings are given in quanti-

ties of six to ten ounces every two hours. Diluted egg albumin alone often allays the severe symptoms. The frequent feedings serve to lower acidity and provide a smooth texture to the gastric contents and prevent trauma to the healing ulcer that might occur when foods of coarse fibrous nature are ingested. The coarse foods damage the growing epithelial coating of the healing ulcer and promote recurrence or delay complete recovery. The modern dietary, consisting of various combinations of raw vegetable and fruit fibers made up in so-called "salads" comprising tomatoes, celery, apples and carrots among other things, is a common cause of persistent gastric symptoms in ulcer patients. The eating of these things by an ulcer patient is comparable to a varicose vein patient treating his varicosities and concomitant ulcers by daily rubs with coarse sandpaper.

Since Marriott [9] in 1929 advocated the use of evaporated milks in the feeding of young children, the senior author, H. W. S., began to employ them in the treatment of gastric and duodenal ulcer and ulcerative colitis. Milk as a source of bacterial infection in human beings, particularly in streptococcus sore throats and other infectious diseases, has been repeatedly emphasized. The work of Rosenow [10, 11] in this regard is highly significant. The splendid experimental work of Saunders [12] in demonstrating that milk is a possible etiologic factor in gastric and duodenal ulcer lends credibility to the belief that milk may possibly be a source of infection to individuals who are susceptible to a combination of factors leading to the development of peptic ulcer. Ross [13] has reported a series of cases of peptic ulcer treated with the evaporated milks. The clinical observations of the author (H. W. S.) suggest that evaporated milks are a helpful adjunct in the dietary management of ulcer patients. Our diet lists have in recent years been modified to contain many raw fresh eggs which supply all the needed vitamins. A preliminary report of these observations has been published by Soper,[14] and a more complete report of clinical observations with evaporated milk will be made later.

The administration of alkalies to ulcer patients has long been a matter of controversy. We no longer employ them extensively. The smooth diet, frequently fed, seems to be the secret of successful management. After two to three weeks on strictly soft foods the patient is permitted coddled eggs, increased amounts of cooked cereals, together with cottage cheese, toast with the crusts removed, creamed vegetable soups, ice cream, jello, baked or mashed potatoes, stewed fruits, white meat of chicken and tender broiled steaks or lamb chops.

A favorite sedative employed for many years with great satisfaction is a small dose of barbital (one grain) combined with atropine sulphate (one five-hundredth grain) together in a capsule with sugar or milk. The atropine is sufficient when taken three or four times daily to relieve pylorospasm, and the barbital is a very mild sedative. This prescription can be taken over protracted periods without harm or oversedation.

The more severe forms of benign gastric ulcer will occasionally require

hospitalization. We have used with great satisfaction trans-gastric feedings by means of the indwelling Levin nasal catheter. The tube is permitted to find its way into the jejunum, and a high caloric mixture is given through the tube, placing the stomach completely at rest. This is the same principle as employed by Balfour [15] in surgical jejunostomy minus the attendant surgical risk. The nasal catheter is usually quite well tolerated by these cases after the first few hours of discomfort.

The above outlined principles constitute the measures which we have employed in the medical management of peptic gastroduodenal ulceration. Fortunately we have been consistently successful and see no reason for changing our methods. Practically all patients can remain ambulant and employed. Bleeding or hemorrhagic ulcer demands more detailed consideration.

Soper [16] in 1931 presented a method of treating hematemesis by means of the retention catheter. Severe hemorrhage from a gastric or duodenal lesion benign or malignant is quite alarming, and often accompanied by shock. Recovery frequently is prolonged. Balfour,[17] Bevan [18] and Lahey [19] all advise against immediate operation but reserve intervention for recurrent bleeding. Practically all writers agree that blood transfusion is immediately indicated in all severe hemorrhages and that morphine hypodermically, blood coagulants, and complete bed rest are all essentials.

The principle of keeping the stomach at absolute rest in order to allay bleeding from it or into it (as in the case of duodenal ulcer or esophageal varices) is physiologically sound, and borne out by practical experience in other comparable hollow viscera such as the urinary bladder. Any quantity of liquid material in the stomach will incite peristalsis and provoke additional bleeding or prevent it from stopping. The gastric wall and neighboring contractile viscera containing bleeding vessels must be absolutely quiet in order to promote clot formation and cessation of the hemorrhage. Nature creates a vicious circle by virtue of the fact that the blood in large quantities escapes into the stomach, excites peristalsis and thereby accentuates the bleeding. This process is comparable to a hemorrhage into the urinary bladder from any source. The bladder fills up with clots and in the attempt by the hollow contractile organ to expell its contents tenesmus, spasm, overactive contraction and congestion are produced and the bleeding is aggravated. The quickest method of relief here is to empty the bladder with a large catheter or an evacuator and place it at rest by an indwelling catheter and keep it at rest. The analogy to hemorrhage into the stomach is entirely logical. In spite of this one hears and reads of the so-called "expectant treatment of hematemesis" which consists of the administration of morphia and of letting the stomach do the best it can to get relief by vomiting or by expelling its contents into the intestinal tract. It is to encourage the wider use of our method of gastric siphonage in the treatment of hematemesis that we wish to present in detail its employment and to reaffirm our satisfaction in its further use.

By this method one has absolute control of the situation in gastric hemorrhage. The introduction of the tube is not uncomfortable to the patient if careful technic is used. The stomach is readily emptied of all clots and placed immediately at rest. Retching and vomiting such as are caused by lavage with a large tube are avoided, to the great satisfaction of the patient. A thromboplastic substance can be given hypodermically to promote coagulation in the bleeding vessel, and the same substance is of great advantage in the stomach itself, for seemingly it not only aids in stopping the bleeding but apparently causes the larger clots to be broken up into fine black particles so that they may be readily withdrawn through the nasal tube. Recurrent bleeding is readily detected by observing the washings, and the presence of acidity may be noted by testing with congo paper. The stomach can then be gently lavaged with a mild alkaline solution of soda bicarbonate to neutralize the acid secretion.

The following detailed points in the employment of this method are worthy of reiteration.

1. The technic of passing the tube is important. The nasal mucous membrane should be shrunk with a 2 per cent solution of cocaine hydrochloride. The Levin nasal catheter with several perforations in the distal six inches should be slowly passed down the esophagus and the patient allowed to take a swallow of water with each short advance of the tube. The glass pistoned syringe should be used often to keep the tube free of small clots. The tube may be permitted to drain by siphonage alone or may be attached to an apparatus to provide continuous suction, such as described by Ward,[20] Wangensteen,[21] Orr [22] and others. The character of the secretion passing through the tube should be observed frequently and tested for acid with fresh congo red paper. Liquid petrolatum is dropped along side of the tube through the nostril three times daily, and if the patient complains of sore throat a spoonful of liquid petrolatum may be given every one or two hours.

2. The use of a local hemostatic is important. We employ thromboplastic solution, injecting it undiluted directly into the stomach after the clots have been removed. The fine black clots that result are characteristic of this hemostatic.

3. The patient is usually thirsty, and we find that fresh egg albumin, water and gelatin water rarely excite acid secretion and can be safely permitted by mouth. Proctoclysis with a physiologic solution of saline and the intravenous injection of 2000 to 3000 c.c. of normal saline containing glucose in 5 to 10 per cent solution are continued for a period of three days. After that time the tube is permitted to find its way into the jejunum. This can be demonstrated by a roentgen-ray film. The patient is then fed a high caloric mixture and the stomach is still maintained at rest for a period of a week or 10 days according to the condition of the patient and the amount of discomfort caused by the nasal tube.

The obvious advantages of the method are its simplicity, and its value

in the removal of clots from the stomach and placing it at rest, the control of acidity, the easy detection of further bleeding, the elimination of nausea and vomiting and the maintenance of the patient's comfort. In addition the tube may be employed to give jejunal feedings and so maintain the stomach at rest for any desired period of time in accordance with the requirements of the individual patient.

Just which cases of peptic ulcer of the stomach and duodenum should be selected for surgical treatment has long been controversial. It is only through intelligent coöperation between the clinician and surgeon that the best interests of the patient are served. It is generally conceded that all uncomplicated cases of simple duodenal ulcer should be treated by a medical regimen, reserving surgical procedures for those cases which do not respond to the more conservative methods. In borderline cases the choice of method is frequently a matter for weighty decision. It is likewise conceded to be justifiable to use a medical regimen in the treatment of benign gastric ulcer. Emphasis must be placed on the dictum that any gastric ulcer which does not show an immediate response to diet and rest with a definite tendency to heal quickly, as shown by competent roentgenography, should be considered potentially malignant and recommended for surgery.

The successful surgical treatment of duodenal ulcer has been a great achievement. Relief of the patient's symptoms with minimal risk should be the goal rather than to subject him to a pre-determined type of operative procedure. It would seem obvious that extensive operations, such as gastrectomy and gastroduodenal resection, will carry a higher mortality in any surgical clinic than the more conservative procedure of gastro-enterostomy. We believe that the acid factor is the most important one in causation of ulcer. The reduction of acidity by a well functioning gastro-enterostomy certainly seems to be the more reasonable and conservative choice of procedure; especially since it is admitted that achlorhydria is secured in but 56 per cent of patients subjected to total or partial gastrectomy. These points were emphasized recently by Klein, Aschner and Crohn.[23]

The choice of operative procedure, then, in duodenal ulcer should be made from a conservative point of view. The selection of procedure should be suited to the individual case and will vary according to the anatomic and pathologic characteristics of the ulcer and of the patient. The position of the stomach in the abdomen and its accessibility at the operating table will also influence the surgeon in his choice. In a series of 129 cases the author (J. W. T.) found it justifiable to perform gastro-enterostomy on 87 patients whereas it was deemed advisable to choose pyloroplasty in but 17 of this series, pyloroplasty of Bilroth I type being employed in five cases. Partial gastrectomy was done in 18 instances for gastric ulcer. In 50 per cent of these the lesion proved to be malignant. The author (J. W. T.) has never deemed it justifiable to perform extensive partial gastrectomy for duodenal ulcer but has conservatively employed the more physiological complete pylorectomy of Bilroth I type in five cases with uniformly satisfactory re-

sults. Walters [24] recently stated that "the case for subtotal gastrectomy with removal of the duodenal ulcer remains one for further study, during which time gastro-enterostomy should continue to hold a position of high regard, for it will give good results at low operative risk in properly selected cases in which the response to a properly carried out medical regimen has been inadequate."

Proper selection of surgical cases requires experience and clinical judgment, and as an aid the following classification has been suggested.

1. Acute perforated
2. Recurrent hemorrhagic
3. Chronic recurrent (with duodenitis—multiple serpiginous ulceration)
4. Obstructive
5. Multiple ulcerative (severe symptoms, short duration, no relief by medical regimen)
6. Chronic perforative (with attachment to pancreas or gall-bladder)

Case reports illustrative of those several types have been made previously by Thompson.[25]

The perforated duodenal or gastric ulcer is of course always a surgical emergency. Shelley [26] reviewed 82 cases in which there was an immediate mortality of 18.3 per cent due to peritonitis and pulmonary complications. His follow-up records of cases were excellent and his statistics confirm the conservative opinion that a single inversion of a perforated ulcer with drainage of the abdomen will save more patients than any other procedure. Adding posterior gastro-enterostomy to the load the patient already carries will in not a few instances be a factor in causing his death. It is only in rare combinations of circumstances favorable to the patient, such as a very recent perforation with actual or impending pyloric obstruction, that gastro-enterostomy should be done simultaneously with inversion. Should obstruction occur later, gastro-enterostomy can be done with minimal risk. Many patients after perforation are strikingly free from symptoms following single inversion. This fact alone condemns the routine performance of gastro-enterostomy in the presence of acute perforation.

The question of closure of such perforated cases without drainage again is a matter of very careful individual judgment and opinion. Closure without a drain in any wound such as a thyroidectomy, radical or simple mastectomy, or cholecystectomy is an ideal which should not be too strenuously pursued. In most cases of perforated duodenal ulcer, or of any other hollow viscus, it would seem advisable to follow the practical old masters who almost invariably drained such cases.

There is no one who will disagree with the statement that obstructing duodenal or pyloric ulcer patients should be treated by appropriate surgical procedure such as gastro-enterostomy, pylorectomy or gastro-duodenostomy. The results obtained by gastro-enterostomy in this type of case have been uniformly satisfactory. It is the duodenal ulcer patient without obstruction who has long been a subject of controversy between internist and surgeon.

It is a very serious mistake and an absolutely unjustifiable policy to deny surgical relief and cure to those unobstructed patients who have chronic or severe acute symptoms unrelieved by an adequate medical regimen. Such patients suffer intensely and should demand surgical treatment if and when they fail to get relief of their symptoms by medical measures such as diet, sedation, alkalies and rest in bed.

TABLE I

Results Following Various Surgical Procedures for Peptic Ulcer

Operation	No. of cases	Symptom free	Incomplete relief	Hospital deaths following operation	Per cent operative mortality	Remarks
Gastro-enterostomy	87	80	Persistent mild dyspepsia 7	2	2.3	Deaths due to vicious circle and intestinal obstruction
Pyloro-plasty	17	16	Recurrent bleeding 1	0	0	Patient with poor result (bleeding) refused re-operation
Bilroth I pyloroplasty	5	5	0	0	0	All patients entirely free of symptoms
Closure of perforation and drainage	20	12	3	2	10	Deaths from peritonitis due to delayed operation
Excision of jejunal ulcer	1	1				Followed gastro-enterostomy done elsewhere in presence of acute perforation
Gastric resection	18	16	Complain of peristaltic rushes 2	1	9.2	Eight patients proved to have malignant ulcer
Total cases	148	Approximately 90% complete symptomatic relief 130	Approximately 10% incomplete relief or poor results 13	5	3.1	Average per cent operative mortality

The severe burning pain which is unrelieved may be a precursor to perforation which will demand emergency surgery under adverse circumstances at great risk. Many duodenal ulcer patients will present themselves with hyper-motility, hyper-peristalsis, severe pain and pylorospasm. These persistent symptoms will frequently require surgical relief after medical failure.

The choice of operative procedure in such patients is of great importance. Some type of pyloroplasty can frequently be used to advantage. This operation is more physiological in that it empties the acid gastric contents into an area of high alkalinity which is biologically designed to receive them. The fearful complications of gastro-jejunal ulcer are avoided. It is, however, not always technically possible to perform pyloroplasty or pylorectomy with minimal risk. Gastro-enterostomy when properly performed will give symptomatic relief to the majority of such patients who suffer from chronic (non-obstructive) single or multiple ulceration of the duodenal mucosa.

The term "complicated duodenal ulcer" has been frequently used to designate those cases which do not obtain relief by medical regimen. This terminology is acceptable, but one cannot accept the viewpoint that a patient without organic obstruction or gastric motor insufficiency is to be advised against surgical treatment. Such advice is bad and can only be accounted for by a misconception of the pathologic changes in the duodenum which accompany peptic ulceration.

Peptic ulcer of the gastric mucosa should always be considered potentially malignant. The majority of benign gastric ulcers quickly heal under a careful dietetic and sedative regimen. Occasionally a stubborn case will require hospitalization and jejunal feedings by the Levin trans-nasal duodeno-jejunal catheter. In the event that an immediate response to treatment does not result, then all gastric ulcers no matter what their size or location should receive the benefit of surgical exploration. Total gastrectomy, while a formidable procedure carrying a relatively very high mortality rate, has been successfully performed many times by competent gastric surgeons. Gastric cancer even when viewed through rose colored glasses is still a very grim spectacle. While extensive resections are possible, recurrences are frequent and permanent cures are few. These facts should not deter one from advising surgical exploration of all suspicious gastric ulcers.

The postoperative management of gastro-duodenal surgical patients is made much easier by the routine use of the Levin nasal catheter with continuous suction siphonage. This method is far superior to the intermittent gastric lavage by means of the large caliber tube. One can determine just when the gastrointestinal tract begins to function. The patient's stomach is never allowed to fill with secretions or liquids, and gastric dilatation is prevented. Nausea and vomiting are almost entirely eliminated by intelligent use of this method which we have employed since 1928. Routine administration of carbon-dioxide inhalations aids in preventing postoperative pulmonary atelectasis. The diet is increased gradually about in accord with the methods employed in the treatment of acute medical cases. Following surgical dismissal all patients are carefully followed up by the clinician who strongly warns them against dietary indiscretion.

These patients can eat a liberal variety of foods but must not be permitted utterly to disregard the knowledge that their gastro-duodenal physiology is not perfect or they would not have developed peptic ulcer; therefore, they

must use caution in their gastronomic behavior following surgical procedures.

The teeth, tonsils, paranasal sinuses, cervix, prostate gland are all to be considered possible sources of focal infection and such infections should be eliminated by appropriate methods if found to be present. These patients should always be considered as possessors of physiologically abnormal gastrointestinal tracts and warned to temper their habits with discretion.

Summary and Conclusions

1. The best interests of the peptic ulcer patient are served by combined medical and surgical judgment.

2. The superiority of the trans-nasal suction siphonage in the treatment of gastro-duodenal hemorrhage is emphasized.

3. A series of surgically treated peptic ulcer cases is reported in tabular form.

4. A very careful postoperative dietary and hygienic regimen is essential in securing permanently good results.

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OBSERVATIONS ON THE EFFECT OF SUDDEN CHANGES IN ARTERIAL TENSION IN ANGINA PECTORIS *

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Angina pectoris is generally considered to be a manifestation of diseased coronary arteries. Coronary sclerosis is present in most cases but not in all, and marked coronary sclerosis may be found in cases which have not shown the anginal syndrome. To account for the cases with little or no pathological findings the theory of coronary spasm has been advanced.[1, 2, 3] This is also a possible explanation of the angina of rest. The finding of changes in the R–T segment of electrocardiograms taken during spontaneous or induced attacks [4, 5, 6] has been considered confirmatory evidence of the occurrence of coronary spasms. It is known, however, that changes in the R–T segment may occur in coronary thrombosis without pain. Similar changes have been produced by exercise in patients with angina pectoris, without precipitating an attack of pain.[6] Such changes have also been reported in rupture of the right auricle [7] and have been produced experimentally by injecting various substances into the pericardium.[8]

It has been found that the coronary constrictor mechanism is poorly developed in animals,[9, 10] and the suggestion has been made that a failure of the dilator mechanism may account for some cases of angina pectoris. Wenckebach [11] believes a failure of the depressor mechanism is responsible for a sudden increase in aortic pressure and that this is the mechanism of attacks in certain cases which he designates true angina pectoris, as distinguished from coronary sclerosis.

The nerve control of the coronary circulation has not been definitely worked out. The vagus is probably the coronary constrictor and the sympathetic the coronary dilator.[12] The reverse is true in the peripheral vascular system. Drugs that constrict the peripheral vascular system frequently precipitate attacks of angina pectoris, and dilator drugs usually relieve the pain. These drugs may act through a local effect on the blood vessels rather than through the nerve mechanism.

The purpose of this study was to demonstrate a possible change in the coronary circulation by a physical stimulus to the vascular system that did not entail any physical effort and that was free from any local effect on the coronary vessels. The "Cold Pressor Test" of Hines and Brown [13] admirably fulfills these requirements. It produces in most instances a marked vaso-constriction demonstrable by an elevation in blood pressure. This is usually accompanied by a slight increase in the pulse rate, which suggests a widespread effect on the sympathetic system. If coronary spasm is a factor in producing attacks of angina pectoris, it is an abnormal reaction due to an

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irritability of the vascular system in the heart. Consequently it seemed reasonable to suppose that in some cases attacks would follow the application of this test.

Method

A modification of the cold pressor test was used. The left hand was immersed in a large basin of water at a temperature of 6° C. and was kept in the water until the test was completed. The blood pressure was taken on the right arm at least 14 times. A cardiogram was taken immediately before and at the height of the blood pressure reaction. Only one lead was taken during the test and in most instances this was a chest lead with one electrode on the anterior chest, just inside the apex, and the other on the left leg. The subject was questioned before and after the test in reference to pain in the chest.

Material

Sixty-four patients with angina pectoris were subjected to this test. There were 46 males and 18 females. Thirty-two cases had normal blood pressure, 27 were hypertensives and five were hypotensives. All 64 cases had angina of effort. Ten had both angina of effort and rest. Five conformed to Wenckebach's description of true angina. Seventeen cases had definite histories of coronary thrombosis. The following table gives the age of the patients and the duration of the disease:

Table I

Angina Pectoris: Duration of the Disease, and Age of the Patients

Duration	1 yr. or less	1 to 3 yrs.	3 to 5 yrs.	5 to 8 yrs.	10 yrs. or over
No. of Cases.....	28	14	10	9	3
Age	30 to 39 yrs.	40 to 49 yrs.	50 to 59 yrs.	60 to 69 yrs.	70 to 79 yrs.
No. of Cases.....	1	6	24	26	7

Results

Figures 1, 2 and 3 show maximal systolic and diastolic blood pressure reactions to the cold pressor test of the entire group. There was comparatively little difference between the reactions of the anginal patients with normal blood pressure and the hypertensives. The maximal reaction in the hypertensive group was 82 mm. systolic and 45 mm. diastolic. The maximal reaction in the anginal cases with normal blood pressure was 74 mm. systolic and 40 mm. diastolic. Fifty-three per cent of the angina pectoris cases with normal blood pressure had a "ceiling" or maximal rise in systolic pressure of 150 mm. or more. The average rise in this group was 29.84 mm. systolic and 16.53 mm. diastolic. A group of 41 cases with normal blood pressure were subjected to the same test. This group was composed of normal in-

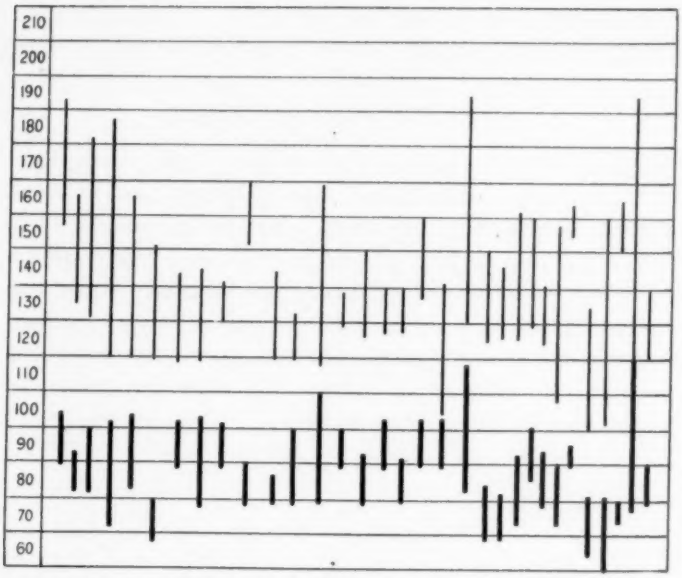

FIG. 1. The maximal systolic and diastolic changes in blood pressure during the cold pressor test in 32 angina pectoris cases with normal blood pressure. (Heavy lines denote diastolic pressure.)

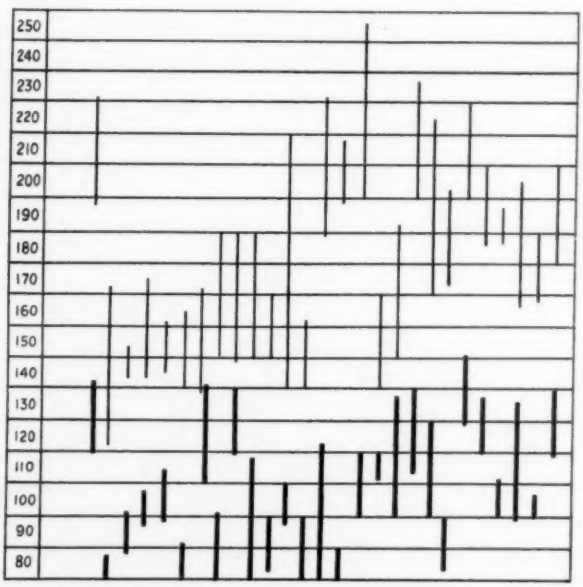

FIG. 2. The maximal systolic and diastolic changes in arterial tension during the cold pressor test in 27 hypertensive angina pectoris cases. (Heavy lines denote diastolic pressure.)

dividuals, cases with cardiac neuroses and cardiac diseases, other than angina pectoris. Fifty-three per cent showed a "ceiling" of 150 mm. or above. The average rise in pressure was 32.63 mm. systolic and 18.29 mm. diastolic. It is possible that some cases in both groups have had hypertension in the

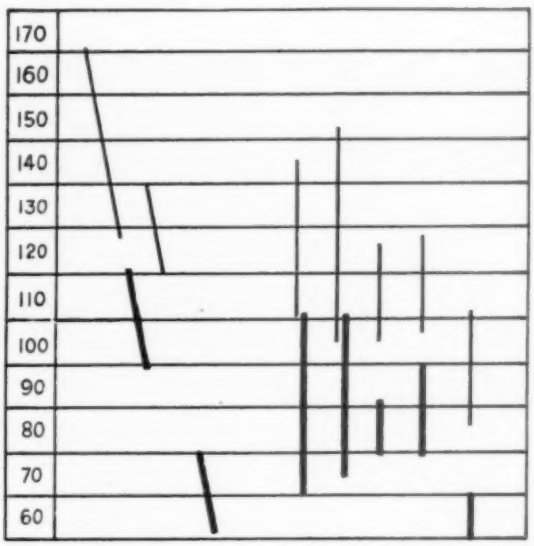

FIG. 3. The first four lines (slanting) represent the drop in pressure in two cases of angina pectoris that had a reverse reaction. The other 10 lines (straight) represent the increase in pressure in five hypotensive angina pectoris cases. (Heavy lines denote diastolic pressure.)

past, but it was impossible to prove it. There were two cases shown in figure 3 that had a reverse reaction, a precipitate drop in blood pressure, with a slowing of the pulse rate, pallor and sweating about the face and head.

ELECTROCARDIOGRAPHIC FINDINGS

Sixty-two cases that did not have anginal symptoms were used as controls. There were 10 hypertensive cases. Nine averaged a rise of 39.2 mm. systolic and 14 mm. diastolic. One hypertensive case showed a reverse reaction, with a drop in pressure from 170 mm. systolic and 110 mm. diastolic to 118 mm. systolic and 85 mm. diastolic. The average rise in 41 cases with normal blood pressure was 32.63 mm. systolic and 18.29 mm. diastolic. Eleven cases with low blood pressure averaged a rise of 24.81 mm. systolic and 13.81 mm. diastolic.

In this group the changes in the Q, R and T were slight, one mm. or less. There were no changes in the R–T segment. In the 64 angina pectoris cases only 12 showed more than 1 mm. change in the Q, R, S and T deflections during the cold pressor test. One of these cases showed a reverse reaction, with a drop in blood pressure of 38 mm. systolic and 20 mm.

diastolic. The remaining 11 averaged an increase of 39.3 mm. systolic and 15.4 diastolic.

There is nothing characteristic in the changes in the Q, R, S and T's in these cardiograms. Such well-marked changes, however, did not occur in any of the other angina pectoris cases or controls. The changes in the R–T

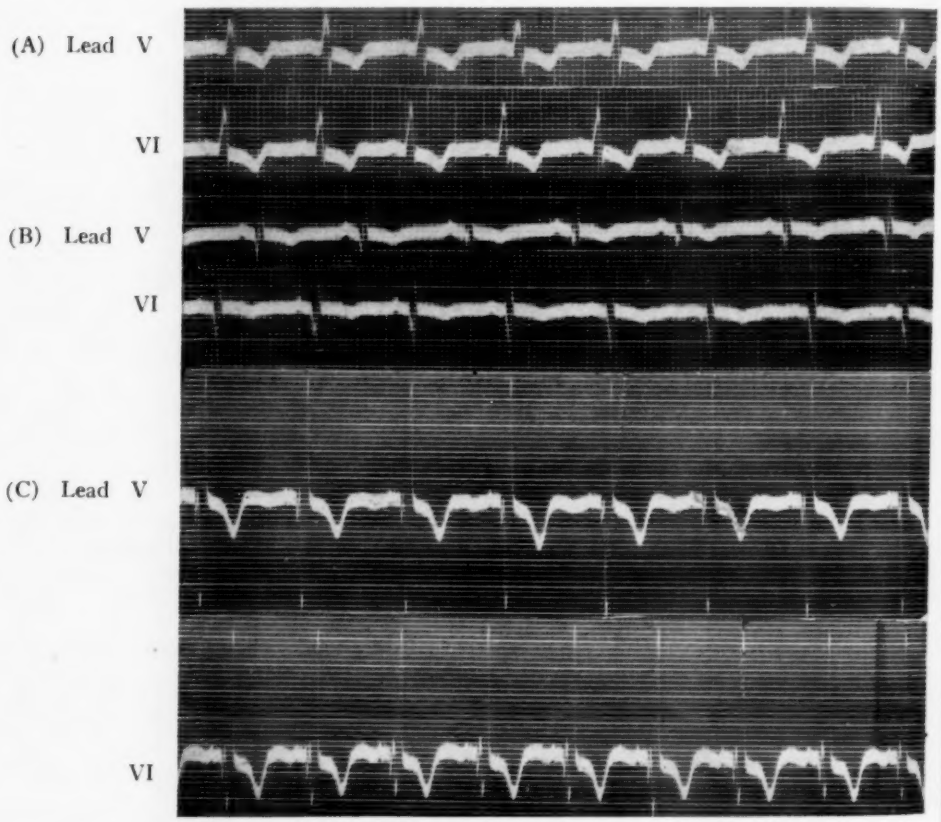

FIG. 4. The first cardiogram in each group is a chest lead (anterior chest, just inside the apex, and the left leg) taken immediately before immersion of the left hand in ice-water. The second is the same lead taken at the high point in the blood pressure. (*A*) Shows an S which is decreased during the ice-water test. The increase in blood pressure was 4 mm. systolic and 5 mm. diastolic. (*B*) Shows an increase in the Q and a decrease in the R during the test. This is a case with normal blood pressure. The increase in pressure was 33 mm. systolic and 25 mm. diastolic. (*C*) Shows a decrease in the Q. There is an increase in the notching and in the negativity of the R–T segment. The T is increased. This is a case of malignant hypertension with an angina pectoris syndrome. The increase in blood pressure was 66 mm. systolic and 20 mm. diastolic.

segment in figure 5 (*a*) and (*b*) are of the type suggestive of coronary obstruction. In figure 5 (*c*) the R–T segment changes from negative to isoelectric during the cold pressor test. Only four cases showed changes in the R–T segment. It seems probable that these changes are significant of a

damaged myocardium. It is not possible to assume that they are the result of coronary spasm.

Pain

Only 11 cases failed to complain of pain in the hand immersed. Two stated that the pain radiated up the left arm as far as the shoulder. Two developed slight shortness of breath and the feeling of oppression in the chest. Three cases that had slight anginal pain in the substernal region before the test were relieved when the hand was immersed in the ice water.

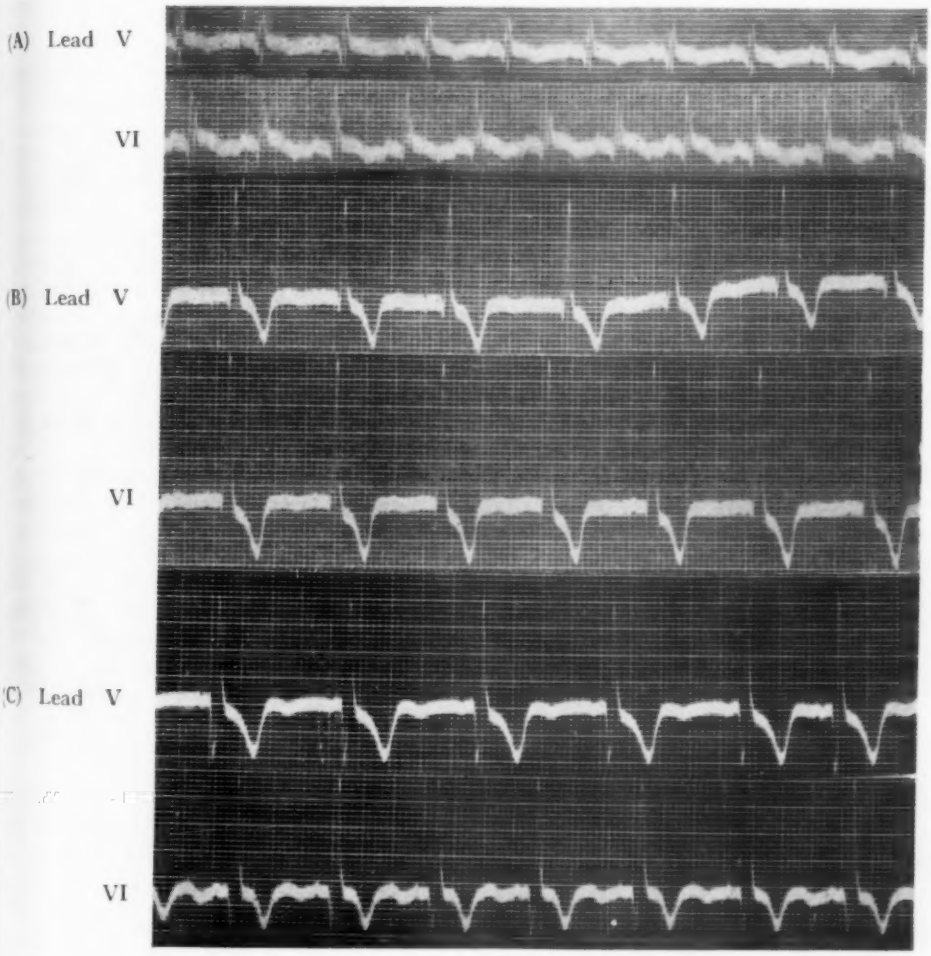

FIG. 5. (*A*) During the ice-water test the R–T interval becomes positive. This individual is a diabetic with angina pectoris and a normal blood pressure. The increase was 48 mm. systolic and 30 mm. diastolic. (*B*) A female with hypertension showed an increase in the systolic pressure of 30 mm. and 10 mm. in the diastolic. (*C*) A hypertensive case. The R is increased, the Q and T are decreased and the R–T segment becomes isoelectric. The blood pressure increase was 50 mm. systolic and 25 mm. diastolic.

Two developed a pulsus alternans during the test. Four cases showed frequent premature beats that were not present before the test. One case developed a typical attack that gradually subsided when the hand was removed from the water. The pain was in the substernal region and radiated to the back and both arms. The increase in blood pressure during the cold pressor test in this case was 35 mm. systolic and 25 mm. diastolic. The cardiogram which was taken during the attack failed to show any change in the complexes or in the R–T segment. At a later date the carbon dioxide test was used on this case with an increase in blood pressure from 204 mm. systolic and 120 mm. diastolic to 240 mm. systolic and 150 mm. diastolic. This failed to induce an attack.

Case Report

A married woman, 57 years of age, of normal appearance, had lived in Florida for the past 20 years. The family history was negative. There were no known hypertensive cases in the family. She had pleurisy two years ago and malaria one year ago. She stated that her blood pressure was elevated two years ago but did not know how long it had been elevated.

Her chief complaint was pain in the substernal region, radiating to both arms and to the back, precipitated by exercise, excitement or contact with anything cold; relieved by immersing the hands in hot water and by nitroglycerine. She first noticed these symptoms five years ago. Handling ice, eating ice cream, drinking ice water, even standing in front of the open door of an electric refrigerator will precipitate the pain. She discovered a year ago, while washing dishes, that hot water relieved the pain and since then has been immersing the hands in hot water for immediate relief. For the past year walking one-half to two blocks has produced pain in the calves of both legs, which is relieved by standing still for a few minutes.

Examination. She was five feet tall and weighed 130 pounds. The teeth, throat, neck, thyroid and sinuses were negative. The reflexes were normal. The skin was normal. The temperature, pulse rate and respirations were normal. The blood pressure was 225 mm. systolic and 135 mm. diastolic, sitting; 230 mm. systolic and 140 mm. diastolic, lying; 192 mm. systolic and 125 mm. diastolic, standing; and 208 mm. systolic and 130 mm. diastolic, after 50 steps. The radial arteries were palpable, grade one. The retinal arteries showed the early changes of hypertension. Pulsation was not felt in the dorsalis pedis and posterior tibial arteries of either foot. The urine was negative. The abdomen and chest were normal. The heart was slightly enlarged to the left and the substernal dullness of the second space was increased. No abnormal sounds were heard, except an accentuation of the aortic second.

Frequent observations over a period of eight months showed a variable blood pressure ranging from 170 mm. systolic and 110 mm. diastolic to 225 mm. systolic and 135 mm. diastolic. On restricted activities and theobromine she has passed a whole month without pain in the chest. During the cold weather this winter, however, she had anginal pain at frequent intervals. Two electrocardiograms, made six months apart, failed to show any abnormalities or change in the complexes.

Comment

In the 64 cases studied it is apparent that sudden changes in blood pressure, either a rise or a drop, of short duration and without muscular effort, failed to precipitate attacks of pain. The three cases that had pain in the

chest which was relieved by the cold water suggest an improved coronary circulation, either through the increased blood pressure, or, possibly dilation of the coronaries. However, the pain in the hand while in the cold water may have over-shadowed the mild substernal distress.

The explanation of the cardiographic changes is not so apparent. The Q, R, S and T changes probably have no specific bearing on this problem, though they were not found in other types of heart disease. Of the four cases showing changes in the R–T segment two were suggestive of coronary occlusion. In one of these a similar change was not produced at a second examination. It seems unlikely, however, that this change was the result of coronary spasm since there was no pain, though the criterion of pain is not decisive. The most plausible explanation is the effect of the increased pressure on a diseased myocardium.

In the case that developed an attack during the test, it is apparent that the elevation in blood pressure was not the precipitating factor. Total absence of electrocardiographic changes suggests that coronary spasm did not occur but is not definite proof. In a vasomotor system acutely reactive to cold, it is conceivable that this might reflexly initiate a coronary spasm that failed to show in the cardiogram. The only other possible explanation is that the pain is due to some abnormal condition in the nervous system and is entirely independent of the cardiovascular system.

Summary

1. Sixty-four angina pectoris cases were subjected to the cold pressor test. In one case a typical anginal attack was precipitated by the test.

2. A chest lead was done as nearly as possible at the height of the blood pressure reaction in all 64 cases. Only 12 cases showed well-marked changes in the cardiogram.

3. The failure of extensive peripheral vasoconstriction to initiate attacks of angina pectoris suggests that the cause of such attacks lies in a failure of the vasodilator mechanism rather than in a coronary spasm or in the nervous system.

4. An unusual case is reported in which attacks are precipitated by contact with cold in the absence of physical effort and are not dependent upon changes in arterial tension.

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THE PRACTICAL USE OF HOBBIES IN THE PRACTICE OF MEDICINE *

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IT is my purpose in the following pages to discuss those conditions in which hobbies are a rational and necessary method of correction; and to point out that the discovery or development of hobbies for patients suffering from certain types of diseases should be more fully recognized as a definite and distinct type of treatment. Hobbies should be studied in regard to the form used, the type administered, the indications and contraindications, harmful effects, and other points of interest so that the results may be observed and controlled as in any other type of treatment.

First let us establish a definition for the term because it is necessary to have a clear conception of a tool before it becomes usable. The medical dictionary and three encyclopedias to which I had access did not even list the term. In Webster's dictionary it is defined as "a subject or plan to which one is constantly reverting; a favorite and ever recurring subject of discourse, thought, or effort; a topic, theme or the like (considered as) unduly occupying one's attention or interest." Evidently, when that definition was composed, a hobby was ascribed very little worth or even desirability. Since that time the need for some recreation or play in the life of everyone has become more generally recognized. Recently the "Leisure League of America" was organized in order to spread the doctrine of play and assist in the choice of workable hobbies. They have already published three excellent booklets and have outlined a very promising series to follow. The first, "The Care and Feeding of Hobby Horses" by Ernest Elmo Calkins, with an excellent bibliography compiled by Hugh Brotherton, is most informative. With this newer, broader view in mind and with especial regard to its application in medicine, I have with a great deal of temerity constructed the following definition paraphrasing Gaskell's description of the action of the heart muscle. "A hobby is the activity in one's life, either physical, mental or both, which possesses the power of rhythmically creating a stimulus to equalize and balance life and to divert it from the overutilization of its powers towards the securing of food, clothing and protection and the accumulation of worldly goods; it enables the possessor to receive all stimuli with a broader and less fatigued outlook; to respond to these stimuli with more poise and judgment; to convey these stimuli throughout life from activity to activity; and maintains throughout one's life a certain ill-defined condition called tone." This, I hope, pictures more nearly the practical, usable therapeutic agent.

In the practice of medicine there has been a general increasing emphasis

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on the value of preventive medicine. This has brought about a closer contact with those not already stricken with disease. In the endeavor to maintain uninterrupted, happy, healthful living and promote longevity, the beneficial effect of a well regulated life, without unnecessary worry or undue mental tension and with the proper exercise, rest and fresh air, is worthy of consideration. The accomplishment of such a state could be aided by the development of a suitable hobby and would, I believe, greatly reduce the future number of some diseases such as certain types of psychoneuroses, gastrointestinal tract disorders, and cardiac diseases. And with the public's growing regard for a periodic check-up by a physician, more and more opportunity will be furnished the medical profession for preventive measures. To the knowing eye of the physician many a person is climbing the ladder of success so intently that he sees only the rungs underfoot and will crash to the ground before he realizes that the angle of inclination is too steep for him ever to reach the top. On the other hand the physician also sees the type of patient who has never attempted to climb, bound by the monotony of existence, his life so dull and tedious that he has never even seen the ladder. Both types of patients, the over ambitious and those lacking in ambition, need a hobby as definitely as others need relief from constipation.

Rest, either absolute or at intervals, is an important factor in the successful treatment of many diseases. First there must be rest in the physical sense. In the case of an irrational patient, cessation of motion may be forced by a sufficient number of attendants and a restraining sheet. Except in such cases few would feel the rest obtained was beneficial. Obviously, mental acquiescence is necessary to physical repose. If, passing beyond this stage of mental acquiescence, real mental relaxation can be reached, with the physical being rested because it is dissociated (so to speak), and the mind happily and peacefully occupied, then we have achieved the state of real rest. Here again a hobby is a vital factor in securing desired results.

In diseases such as typhoid fever, streptococcic septicemia, influenza, scarlet fever, acute tonsillitis, acute bronchitis, and acute nephritis, the patient is acutely ill and adequate rest is indispensable. A hobby, at first probably entirely mental, then during convalescence involving both mental and physical activities, is a real therapeutic agent. Pulmonary tuberculosis (post-sanatorium care), chronic cardiac insufficiency, angina pectoris (interval treatment), arthritis, and hysteria may be cited as a panorama of the chronic diseases demanding more prolonged treatment. Securing necessary rest in this group is often a difficult task. The physician's advice should not be filled with " don'ts " which may lead to mental anxiety and physical restlessness. Here, then, skillful guidance is essential. Hobbies to divert mental tension or to replace mental idleness, to increase or decrease activity, can be used as a definite therapeutic measure.

As in any other types of treatment certain fundamental principles can be laid down for guidance in prescribing hobbies.

Above all the choice of a hobby must come from some deep-seated in-

terest within the patient himself. A school teacher, with an interesting and colorful exhibit at the end of the term in mind, was greatly disappointed in the following choices of her pupils: cigar bands, movie stars' pictures, marbles, match boxes, and hat bands with slang expressions. But, since they were, for some obscure but real reason in each case, that pupil's genuine choice, substitution would have been an error. This illustration from the schoolroom, showing children's natural selection of hobbies in the purest form, also brings out clearly that hobbies are personal interests and not mere fads; not things done to be keeping up with the Joneses; not necessarily beneficial in a commercial sense; and things that cannot stand unskillful handling or too much analyzing.

It is most pertinent that this discussion be illustrated by the hobbies of childhood and adolescence because many of the hobbies of mature men and women are a continuation of, or a resumption of, some interest acquired in youth. Guidance and helpful aid will help many a person uncover innate desires or fancies and lead to the discovery of "an instinctive something that needs but an inner consciousness of its existence to be fanned into a flame of glowing warmth that will sustain him against the cold realities of life." [1] Then it will transport the patient out of his tedious routine and be his mitigating shock absorber.

When helping in the choice of a hobby, or when attempting to uncover those deep-seated but long-suppressed interests, it is necessary to study the inherent nature of the person in question. At one stage of our development collecting is a major interest often establishing habits and interests which are retained throughout life. For those there are many and varied choices, from paintings to canning recipes and back through butterflies, Victrola records, autographs, stamps, pieced quilts, post cards, pipes, embroidery stitches, early American bottles, guns, clocks, old maps, stuffed animals, and etchings.

There is a large group of people engaged in some business or profession who yearn to work with tools and their hands. Too often the unfortunate regard of parents for "white collar" jobs has forced a boy with the making of a first class mechanic or cabinet-maker to end his days as an unhappy, third rate bank clerk or insurance collector. On the other hand, others happily and successfully engaged in the bond business or practice of law have a mechanical turn. People of these types may find relaxation in a basement work shop making ship models or doll furniture or reconditioning old furniture. These hobbies would come under the general classification of "making things" [2] which includes the arts and crafts; wood-carving, painting with water colors, making marionettes, landscape gardening, carving soap models, crocheting, photography, weaving, making models of airplanes, hooked rugs, building boats, taxidermy, and the like.

Another group of persons is interested in more active pleasures: golf, baseball, polo, racing, walking, coasting, bowling, foxhunting, fruit raising,

bee culture, training dogs, cruising, raising carrier pigeons. These would come under the general head of "doing things." [2]

At the other extreme are those who like to retire from action and are happiest surrounded by books, engaged in research or some intellectual feat such as translating Dante from the original or following Einstein through the theory of relativity. The hobbies for these could come under the general classification of "learning things," [2] which would include: history of railroads, astronomy, study of birds, chemical experiments, tracing one's ancestors, study of ferns, and following Byrd's expedition to the South Pole.

The flexibility of hobbies or the group of allied hobbies centering around most subjects of interest must be kept constantly in mind. For example in the case of a patient who is interested in boats there is a wide range of activities enabling one to choose that phase best suited to the case. The patient who is confined to his bed or room or who enjoys quieter pursuits may follow stories of the sea, either reading to himself or listening to someone else; or he may collect pictures of various types of boats or ships. The man financially unable to buy the materials for a real boat or to take time off from work for long trips may enjoy making ship models. The man of means who is interested in boats but unable (either in fact or imagination) to leave his business over long enough periods for sea voyages may find relaxation in a collection of paintings or etchings of ships. Another patient may spend long and happy hours tinkering with an antiquated engine in a battered motor boat and never envy his richer neighbor with the perfectly appointed yacht.

Fishing, in itself, brings activity of mind and body, fresh air, and change of surroundings. When moderate exercise is indicated, the patient can be limited to fishing from the bank of a stream or from a power boat. Trout fishing or deep-sea fishing provide more strenuous activity. For those for whom actual fishing must be prohibited or who are not within easy reach of a stream or sea-port, there are the collecting of rods and flies, mounting specimens, painting or kodaking fish, making flies, reading books on fishing, and the study of fishing grounds. These various phases allow great range in activity, time spent, and financial outlay.

It is usually best that a hobby not be too closely related to one's vocation. When a bank cashier leaves his work after a day spent indoors with ledgers and figures, a ten-mile drive in search of an antique comb-back, Windsor chair reported seen in a Negro hut, provides fresh air and physical exercise as well as relaxation and stimulation. Recently, many of us were startled by the announcement that the King of England knits and crochets scarves and mufflers, but what could be a more restful diversion for one who spends such a large part of each day hurrying from corner stone laying to opening of a hospital speech and constantly in, or rather before a crowd.

A hobby should be chosen with regard to the age of the patient and should allow modification as age increases. A man who spends his vaca-

tions climbing mountains at the age of thirty in later years will have to content himself with arranging his snap shots in scrap books or following the ventures of others. This may often be provided for by choosing a series of allied hobbies, the more active ones leading into the less strenuous as time passes. On the other hand as age increases leisure time usually increases, and a man or woman who starts a stamp collection early in life may allow more and more time to it as years pass. Thus both the collection and the interest may grow apace until the classification and arrangement of the collection, attending auctions, reading pamphlets, books and catalogs, and comparing notes with other enthusiasts fill with delight what for many is a wretched void.

Of course, one consideration behind every choice is the patient's financial condition. But here again alteration is usually possible. The man with limited means naturally cannot collect old masters. But he can find excellent reproductions well within his means. The woman who is a garden enthusiast may not be able to buy imported bulbs but she can still create a bit of satisfying loveliness with tamed donations from nature.

The physician must not be surprised or discouraged if his patient suddenly loses interest in a hobby he has been following either from choice or at the physician's suggestion. Neither should it be pushed, but dropped, and new interests found in the same way as one would not prescribe quinine for a patient with a known idiosyncrasy to the drug. As in any other procedure which the physician adopts, his interest and skill will increase with continued use.

It has been said that " The knowledge which a man can use is the only knowledge which has life and growth in it and converts itself into practical power. The rest hangs like dust about the brain or drops like rain drops off the stones " (Froude). How often in medicine recurs the advice " Help the patient develop a hobby," or " The patient should find a hobby," but because of the vague conception of the term in the minds of both patient and physician and the lack of practical suggestions this excellent therapeutic measure often fails to " convert itself into practical power." It is hoped that this paper has shown that helping develop a hobby is both practical and simple with only a few general rules and underlying principles to be considered.

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CASE REPORTS

PROLIFERATIVE INTIMITIS OF SMALL ARTERIES AND VEINS ASSOCIATED WITH PERIPHERAL NEURITIS, LIVEDO RETICULARIS, AND RECURRING NECROTIC ULCERS OF THE SKIN *

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The various types of occlusive vascular disease produce clinical pictures which may vary greatly with the extent and situation of the lesions and the rapidity with which they develop. However, certain clinical and pathologic entities have been established and although their exact etiology still remains obscure the diagnosis usually is not difficult. This case is presented because of its unusual clinical and pathologic features which do not conform to any of the more common syndromes.

One of the outstanding features of the case was the marked degree of livedo reticularis. This is a descriptive term which has been given to a permanent bluish-red, retiform mottling of the skin of the extremities and frequently the trunk also. According to Williams and Goodman, the basis for livedo reticularis, also called livedo racemosa and generalized telangiectasis, is a capillary dilatation or atony which may be primarily functional or may be associated with congenital vascular anomalies or organic disease of small arteries and veins. In 1893, Unna reported a case in which there were multiple ulcers and "chronic phlebitis." Endarteritis of small arteries and endophlebitis of small veins have been found in the skin at biopsy in cases of livedo reticularis, by Stokes, Urbach, Becker, and Ebert. Periarteritis and periphlebitis also have been noted occasionally. No extensive pathologic studies of larger vessels and nerves have been described.

The etiology of the vascular lesions in various cases, which have been reported, has been ascribed to syphilis (Ehrmann), arteriosclerosis (Grosz and Kerl), and tuberculosis of the erythema induratum type (Williams and Goodman). Stokes, Becker, and Ebert have reported cases in which no etiologic factor was apparent. Associated ulceration of the skin was noted also in Ebert's case. The combination of livedo reticularis, recurrent indolent ulcers, severe intractable pain, and acute arterial occlusion of the toes has not been described.

Case Report

History. A man, aged 34 years, formerly a machinist, first came to The Mayo Clinic in October 1932. Eight years before, a diffuse reticulated purplish mottling had gradually developed over all the extremities and to a lesser degree over the trunk.

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This condition had been more noticeable over the lower extremities than it had been elsewhere, and had been markedly aggravated by cold. A short time after the onset, a series of painful sloughing ulcers had developed on both legs; the usual site had been the lateral aspect of the ankles. The patient said that these ulcers had developed without preceding nodules but always in one of the blue patches. New ulcers never

FIG. 1. Photograph of patient at the time of the first observation, prior to lumbar sympathetic ganglionectomy. Note the reticulated mottling of the extremities, and ulceration and scarring of both legs.

had appeared simultaneously on both legs. Healing usually had occurred within 14 to 60 days, regardless of the therapy which had been employed, and had left an atrophic pigmented scar. The Wassermann reactions of the blood and spinal fluid had been negative. In 1928, four years after the onset, while he had been working with white lead as a lubricant, a left peroneal palsy had developed. At this time, lead had been found in the stools and urine, and basophilic stippling had been found in the erythrocytes. The foot drop had disappeared spontaneously when contact with lead had been discontinued, and there had not been any recurrence nor had this episode seemed to influence the mottling of the skin or development of ulcers of the legs.

The patient had also been the victim of two severe attacks of influenza, in 1918 and 1927, and in the latter attack he had observed a disappearance of the livedo during the acute febrile course of the disease. Tonsillectomy had been performed in 1928, without benefit. No familial history of vascular or nervous disease was elicited. There was no previous history of thrombophlebitis or varicose veins.

Two weeks prior to his admission to the clinic, the patient had suffered a sudden acute pain in the right great toe which had become pale and cold and had remained so.

Physical Examination and Laboratory Data. Physical examination revealed a well nourished, rather mentally depressed man. Aside from the cutaneous manifestations, the general examination did not reveal anything abnormal. There was a marked livedo reticularis of arms, legs, and lower part of the trunk (figure 1), without definite purpura or telangiectasis. A moderately deep ulcer, measuring 3 by 4 cm., with a dirty sloughing base and slightly indurated borders, was present over the lower third of the anterior aspect of the right leg, and there were several depressed pigmented scars of the skin of both ankles and legs. The entire right great toe was pale and cold and showed a few small patches of subcutaneous hemorrhage. Pulsations in both radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial arteries were present and of normal volume. There were no postural color changes in the feet, with the exception of the right first toe, which became very white on elevation and excessively red on dependency. There were no varicosities. Repeated estimations of the blood pressure were normal. The Kolmer modification of the Wassermann reaction of the blood and the Kline, Kahn, and Hinton tests were all negative. The Mantoux test was negative. No changes in the bones or thorax were revealed by roentgenologic examination, and the routine studies of the blood and urine did not disclose any abnormality. No lead was found in the urine. Special studies of blood smears did not demonstrate anything significant. A small specimen was taken from the margin of the ulcer for biopsy, but it showed only moderate fibrosis and a slight degree of nonspecific, inflammatory reaction. A special tissue stain for tubercle bacilli did not reveal the presence of these organisms.

Therapy and Subsequent Course. Since there were definite signs of a recent occlusion of the digital arteries of the right first toe, several intravenous injections of typhoid vaccine were administered. These relieved the pain and caused a return of color. There was also some reason for believing that obliterative and vasospastic changes in the arterioles were the basis for both the livedo reticularis and the ulcers. Therefore, with the idea of increasing the blood supply of both toes and ulcer-bearing regions, a bilateral lumbar sympathetic ganglionectomy was performed by Dr. Craig, on October 25, 1932. The ulcer was entirely healed within 15 days after operation. The mottled blue areas became red below the knees and the toes and feet remained warm and dry. No ulcers appeared for four months, the longest remission that the patient had noted since the onset of the disease. However, at the end of that time, they did recur, and an acute arterial occlusion of the left great toe developed. This was similar to that previously experienced in the right great toe, although it recovered more rapidly. Cyanosis, mottling, and sensitivity to environmental cold, of the upper extremities increased so that the patient feared that similar ulcers might develop on the hands.

He returned to the Clinic in August 1933, complaining of new ulcers and of pains in the calves of his legs. The peripheral arterial pulsations again were found to be entirely normal. The feet were warm (34° C.). The livedo reticularis was the same in the legs as it had been before, but it was more marked in the arms, and the hands were cold and slightly cyanotic. An arteriogram (Allen and Camp technic) of the right arm did not reveal any evidence of arterial occlusion. Sufficient typhoid vaccine to give a systemic fever of 104° F. produced an increase of the skin temperatures of the fingers from 28.2° C. to 37.9° C.

Three applications of roentgenotherapy to the ulcerated areas of the legs and six subcutaneous injections of an autogenous vaccine, which was prepared from a culture of the ulcer, were administered. Partly at the patient's request, and as a prophylaxis against a possible ulceration of the hands and arms, bilateral cervicothoracic sympathetic ganglionectomy was performed by Dr. Craig on September 9, 1933, with almost complete relief of symptoms and signs in the upper extremities. During the postoperative convalescence, the ulcers of the legs healed but whether we are justified in ascribing this to therapy other than enforced rest in bed is doubtful.

The patient was discharged in October 1933, but returned for further observation in January of the following year. In the interval between visits, he had been free of ulcers for two months, only to have them return with increasingly severe pain which finally required morphine. On his admission to the hospital at this time, a deep sloughing ulcer, which was similar to the previous ones, but larger, was present over the external malleolus of the left ankle. There was also a small area of discoloration of the right calf, which appeared to be about to break down. A biopsy of this lesion revealed some fibrosis of the corium, but did not reveal any inflammatory reaction. In two arterioles in the cutis there was slight hypertrophy of the media. A roentgenologic examination of the bones of the leg showed only a slight osteoporosis. Seven daily intravenous injections of 20 c.c. of activated sulphur, and six injections of the autogenous vaccine (0.1 to 0.6 c.c.) were given without benefit. Potassium iodide and mercury were administered by mouth, but there was no change. Hot packs and pantocain ointment were applied locally but gave only slight relief from pain. Following this, five injections of 0.4 gm. of neoarsphenamine were administered in three weeks, without noticeable benefit. Wet dressings of potassium permanganate and thioglycerol were employed but no healing followed. The patient was even suspected of producing the ulcers and keeping them from healing, and for this reason, an occlusive dressing, designed so that any tampering could be detected, was applied for two weeks, but the ulcers became larger. A dressing of balsam of Peru and an elastoplast bandage were applied, with a rubber sponge to exert pressure over the ulcer, as advocated by McPheeters and Merkert for the treatment of ulcers, caused by venous stasis, but no appreciable healing resulted, and the pain increased until opiates were again required. The patient became very nervous and mentally depressed, and finally insisted that the left leg be amputated, although he was fully aware that this was no insurance against recurrence of ulcers in the remaining leg. An amputation below the knee was finally performed by Dr. Ghormley, June 28, 1934. Convalescence was uneventful, and the stump healed promptly. The patient returned home in August. He recently has reported that ulceration has recurred in the remaining leg. There has not been any noticeable progression or improvement in the livedo reticularis.

Pathologic Studies. Dissection of the anterior and posterior tibial arteries of the left leg, and their vena comites, did not reveal any evidence of occlusion or gross pathologic changes. However, the walls of both the long and short saphenous veins were extremely thick, and the lumina of these veins were very small. Histologic sections of the base and the margins of the ulcer showed

considerable fibrosis of the subcuticular tissue and a mild degree of inflammatory reaction. There was no evidence of any specific type of granulomatous lesion, but there was chronic ischemia with low grade secondary infection of the tissues. Sections of the toes, particularly the first toe, revealed increase in the fibrous

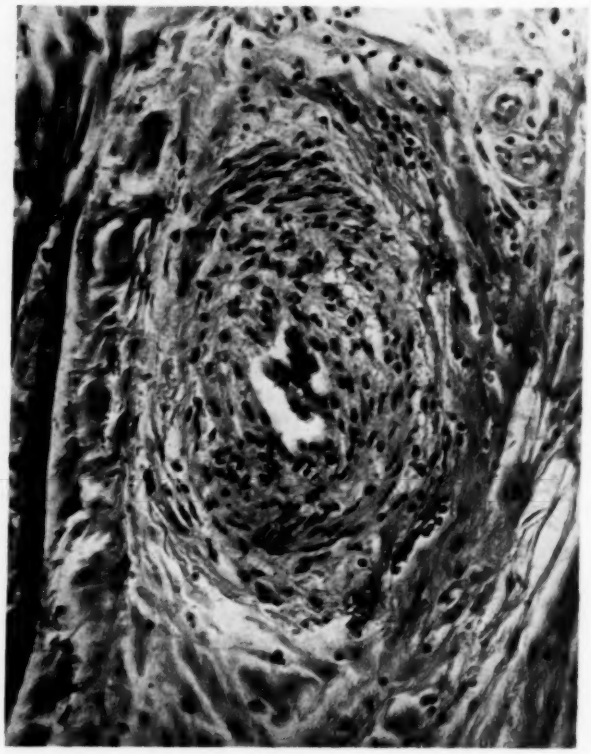

FIG. 2. Photomicrograph of section of small artery from base of ulcer, showing active intimal proliferation. Hematoxylin and eosin stain (× 215).

tissue, and decrease in the fat, with atrophy of the cutaneous glands. The essential histologic lesions were found in the blood vessels and nerves. Sections of the large arteries, such as the posterior tibial, showed slight proliferation of the intima only. However, more extensive proliferation of the intima and definite perivascular fibrosis were found in many small arteries and veins (figures 2 and 3). This was particularly true in vessels which were 200 to 1,000 microns in diameter and situated in the tissue in the base and margins of both the active and healed ulcers. These vessels were situated farther below the cutis than were the vessels in the tissue which was removed at biopsy. In some of the arteries of the first toe, the lumen was occluded by a fibrous mass and there was marked periarterial fibrosis; these apparently represented a late stage of the lesion (figure 4). There was little or no inflammatory reaction in either the media or adventitia of the small arteries and veins. The thickening of the walls of the long and short saphenous veins was almost entirely the result of proliferation of the intima and there was little inflammatory reaction in the wall of the

vein itself (figure 5). Many arterioles (25 to 100 microns) had abnormally thick walls and small lumina; in some, there seemed to be hypertrophy of the muscle and slight proliferation of the intima. In many places, these were surrounded by solid fibrous tissue.

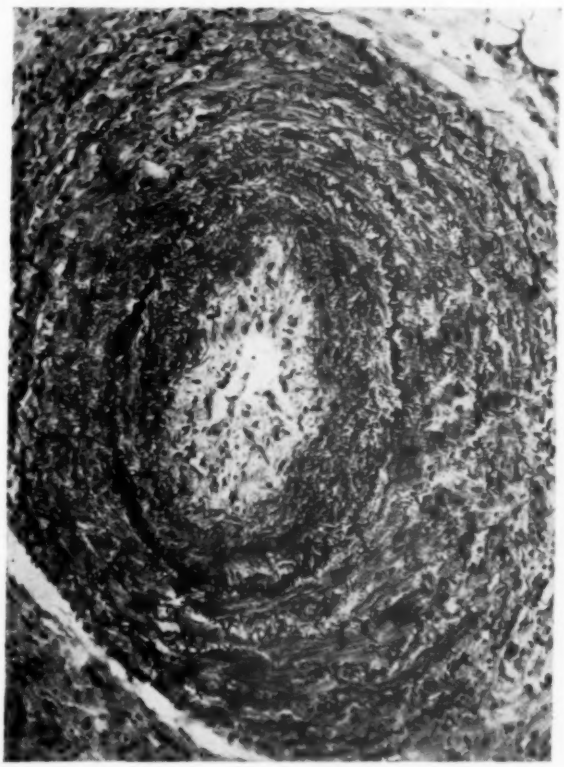

FIG. 3. Photomicrograph of section of small vein near base of ulcer, showing well advanced intimal proliferation and almost total occlusion of lumen, stained with elastin H stain (× 95).

The peripheral nerves all showed perineural and intraneural fibrosis and patchy loss of the myelin sheaths. These changes were only of slight degree in the anterior and posterior tibial nerves and their branches, but were very marked in the long saphenous and sural nerves, in which only a very few myelin sheaths in each nerve bundle took the Weigert stain (figure 6). The vasi nervorum showed the same changes noted in other small arterioles and veins.

COMMENT

In summing up the essential clinical features of this case, we have a young man, aged 36 years, who, for 10 years, had had a permanent livedo reticularis of the legs, arms, and lower part of the trunk, and a series of ulcers of the lower legs, which gradually had become more and more difficult to heal and gradually had become more and more painful in spite of a wide variety of therapeutic pro-

cedures designed to increase circulation and promote healing. Finally, amputation of the leg was necessary because of pain in a large ulcer which could not be healed. There were two episodes of acute arterial occlusion of toes, without definite gangrene or ulceration. There was no evidence of tuberculosis or syphilis. A lumbar sympathetic ganglionectomy seemed to inhibit the formation of the ulcers for a short time only.

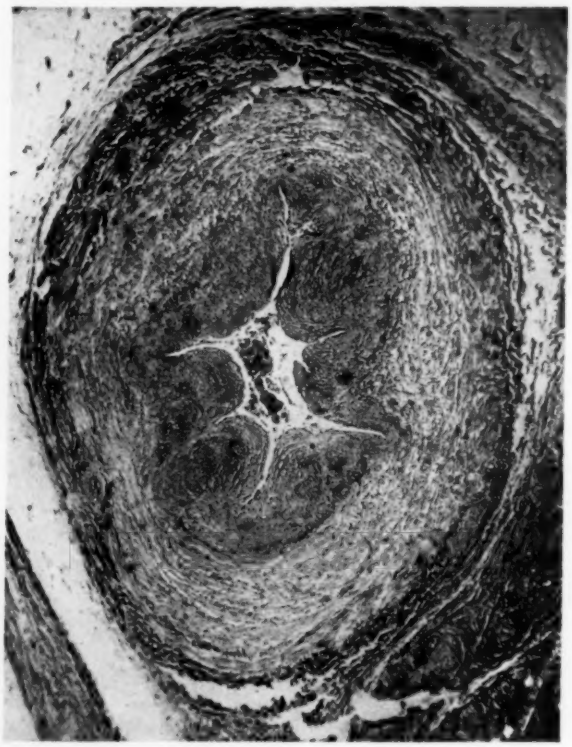

FIG. 4. Photomicrograph of section of long saphenous vein, stained with hematoxylin and eosin. There is marked proliferation and fibrosis of intima, but no inflammatory reaction in media (× 25).

The essential pathologic changes appeared to be a proliferative, occlusive intimitis of small blood vessels, both arteries and veins, and of larger superficial veins. The term proliferative intimitis is used because both arteries and veins were affected and endarteritis and endophlebitis are loosely used in medical literature to denote a variety of vascular lesions. The arterial occlusions produced varying degrees of chronic ischemia of skin and toes and a rather marked degree of ischemic neuritis. There was also a definite thickening of the walls of the arterioles, which possibly was secondary. There was some evidence in favor of an additional factor of venous stasis in the production of the ulcers, because of the fact that veins were obstructed as well as arteries. The pathologic picture of the vascular lesions suggests that they were slow in development and dis-

tinctly different from the lesions of thromboangiitis obliterans, arteriosclerosis, and periarteritis nodosa.

There is no definite clue as to etiology. One would suspect that the proliferative intimitis was a reaction of the vascular endothelium to some chronic toxemia, endogenous or exogenous. There was not any evidence of syphilis, tuberculosis, or other systemic or focal infection. It is noteworthy that the patient had had an episode of clinical lead poisoning four years after the onset of the disease, and it is possible that this contributed to the pathologic changes in both blood vessels and nerves. Whether or not he had had atypical or mild chronic lead poisoning since the onset of the disease is problematical as he had had no known exposure to lead. Subsequently, the condition had been progressive for a long period when he had no contact with lead, none of the typical symptoms of lead poisoning, and had not excreted any lead in the urine. A specific type of vascular lesion produced by lead poisoning has never been adequately described, and possibly does not exist. Certainly, some individuals can have definite clinical lead poisoning without ever having clinical or pathologic evidence of any vascular disease. However, isolated cases of several types of vascular disease have been described in association with definite clinical lead

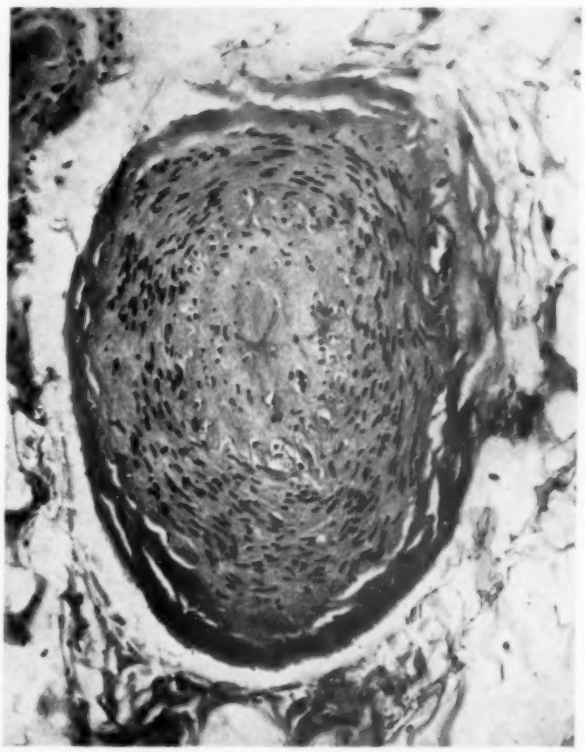

FIG. 5. Photomicrograph of section of small artery of first toe, showing complete occlusion by intimal proliferation with secondary hyaline fibrous degeneration, and periarterial fibrosis. Hematoxylin and eosin stain (× 155).

poisoning; this may be coincidental. The case, described by one of us (Barker) and Brown, as disseminated arteritis of unknown etiology, showed proliferative intimitis of small arteries as well as arteritis and periarteritis of arterioles. There was some, though inconclusive, evidence for chronic lead poisoning in this case, because lead was found in the urine before death, and in certain tissues at necropsy.

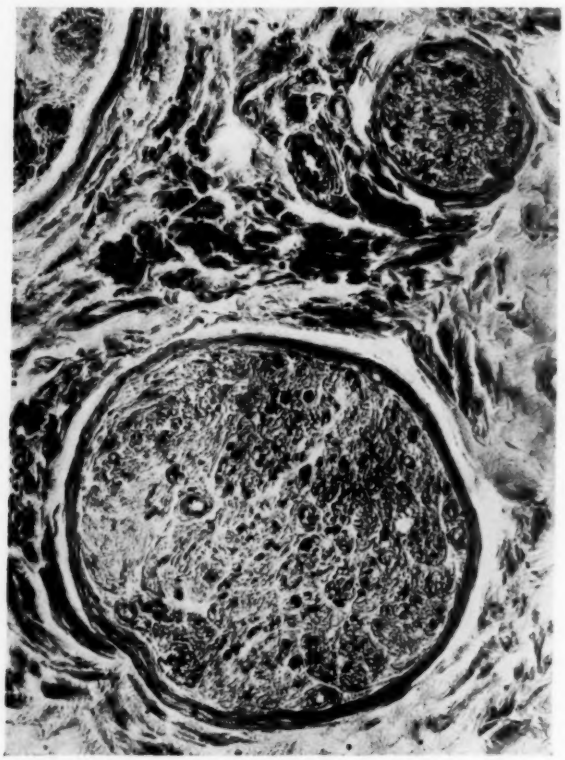

FIG. 6. Photomicrograph of section of portion of long saphenous nerve stained with Weigert's myelin sheath stain. Note disorganization of nerve bundles and only a very few myelin sheaths remaining (× 150).

One remarkable aspect of the case herein reported was its slow but definite progression and refractoriness to therapy. On this basis, the prognosis, both as to loss of other limbs and of life, is uncertain.

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THE BENEFICIAL EFFECT OF THE DEVELOPMENT OF AN ABNORMAL RHYTHM WITH SLOW VENTRICULAR RATE IN CIRCULATORY FAILURE*

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That digitalis medication is often of little value in the treatment of circulatory failure in the presence of persistent sinus tachycardia is well recognized. Digitalis frequently does not slow a regularly beating heart. It has been known since Withering's introduction of the use of the drug that patients with auricular fibrillation respond particularly well to digitalis therapy, and it has been stated frequently [1, 2, 3, 4, 5] that auricular fibrillation in itself is often well tolerated and compatible with satisfactory cardiac function. That patients with circulatory failure may show marked clinical improvement following the development of auricular fibrillation or other abnormal rhythm with a slow ventricular rate has been seldom emphasized or even mentioned in textbooks or articles on cardiac therapy. An exception to this statement is Meakins' recent observation [6] that improvement "is often seen when a rapid regular rhythm which cannot be controlled gives place to auricular fibrillation which can be controlled by digitalis, or when complete heart block develops in a failing heart reducing the rate to around forty. In both of these instances great improvement in cardiac function may be seen."

The following case history is an example of the apparently beneficial effect on the circulation of the replacement of a rapid regular sinus rhythm by auriculoventricular dissociation upon one occasion and by auricular fibrillation later.

Case Report

The patient, a retired merchant, 63 years of age, entered the hospital on February 25, 1933, complaining of shortness of breath upon exertion and at night, at times accompanied by substernal oppression and asthmatic breathing. These symptoms and considerable gaseous indigestion had been present with gradually increasing severity for the preceding six months although the patient had been confined to his home and was taking adequate doses of digitalis. Previous to the development of his present illness he had been well, although he had known for at least eight years that his blood

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pressure was elevated. He had had a gonorrheal infection at 28 years of age but denied syphilis; he had had an appendectomy at the age of 25. His family history was negative except that his mother died of uremia at 73 years of age.

Physical examination revealed a well nourished man, apprehensive, dyspneic and moderately cyanotic. Orthopnea was marked and at times periods of Cheyne-Stokes breathing were noted. There were some distention and pulsation of the veins of the neck, and a heaving diffuse precordial pulsation. The left border of cardiac dullness was 12 cm. from the midsternal line, 3 cm. to the left of the midclavicular line. The heart sounds were of poor intensity with a proto-diastolic gallop rhythm at the apex. The heart and pulse rates were 108. The blood pressure was 170 mm. of mercury systolic and 110 diastolic in both arms. Moist râles were present at the bases of both lungs. The liver edge extended 3 cm. below the costal margin. There was no edema. Other physical findings were normal. The Kahn reaction of the blood was negative. Urinalysis showed a specific gravity of 1.012, a trace of albumin and numerous granular casts. The blood count was normal. The urea content of the blood was 36 mg. per 100 c.c. of blood. The electrocardiogram (figure 1) showed a regular

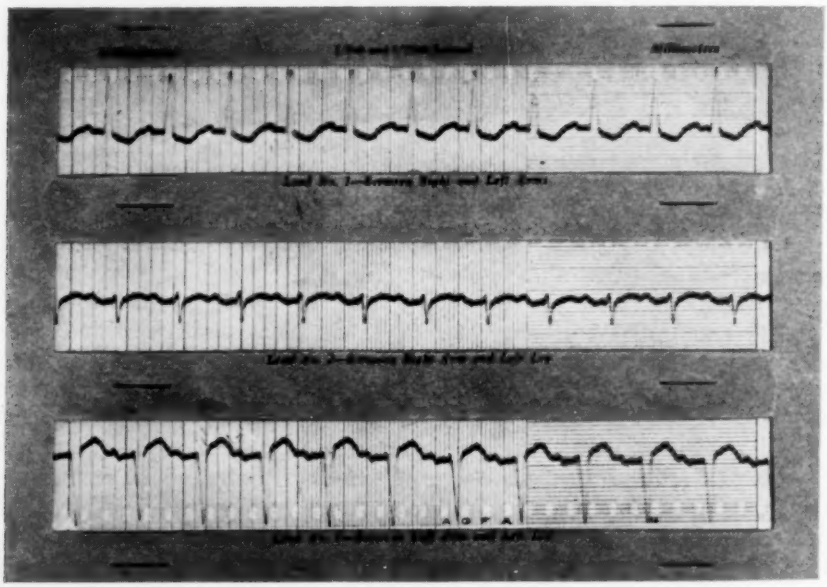

FIG. 1. Electrocardiogram taken on February 25, 1933, during first attack of circulatory failure. Regular rhythm, rate 110, P–R interval slightly prolonged (0.22 sec.), QRS interval 0.1 sec. Marked left axis deviation. Depression of $S-T_1$ and elevation of $S-T_3$ probably due to the marked left axis deviation.

sinus rhythm with a rate of 110, a prolonged auriculo-ventricular conduction time (0.22 sec.) and a QRS interval of 0.10 sec. There was marked left axis deviation with depressions of $S–T_1$, inversion of T_1 and elevation of $S–T_3$. A diagnosis of hypertensive and coronary heart disease with left ventricular failure was made.

For about one month prior to admission to the hospital the patient had been taking powdered digitalis leaves. He had taken three grains for the first five days and then 1 1/2 grains daily. In view of the prolongation of the auriculo-ventricular conduction time it was felt that he was well digitalized and the maintenance dose of 1 1/2 grains daily was continued. Caffein citrate was given every four hours by mouth and was replaced later by caffein sodium benzoate, grains 3 3/4 hypodermically, be-

cause of nausea. Dilaudid, grains 1/32, or morphine sulphate, grains 1/6, was given as necessary to control nocturnal dyspnea and cardiac asthma.

During the first nine days of his hospital stay there was little change in his condition except that he became less dyspneic and the Cheyne-Stokes breathing disappeared while under the influence of caffein. The heart rate continued to be rapid, varying from 90 to 130. There was no significant change in the blood pressure readings. On March 4, because of the development of nausea and vomiting, digitalis was discontinued. It was started again 10 days later with the same dosage of 1 1/2 grains of the leaves daily, but after six days it was discontinued again because of nausea, although the pulse rate was not slowed. He still had severe dyspnea and cardiac asthma at night. Three days later the administration of digalen, 1 c.c. three times daily, was started; after six days the dose was decreased to 1 c.c. twice daily.

Three days later, on April 3, the pulse rate became very slow and irregular. The electrocardiogram (figure 2 *A*) showed a shift in the auricular pacemaker and dissociation of the auricles and ventricles with a slower auricular rate. The auricular rate was 48 and the ventricular rate 66. Occasionally there was a ventricular re-

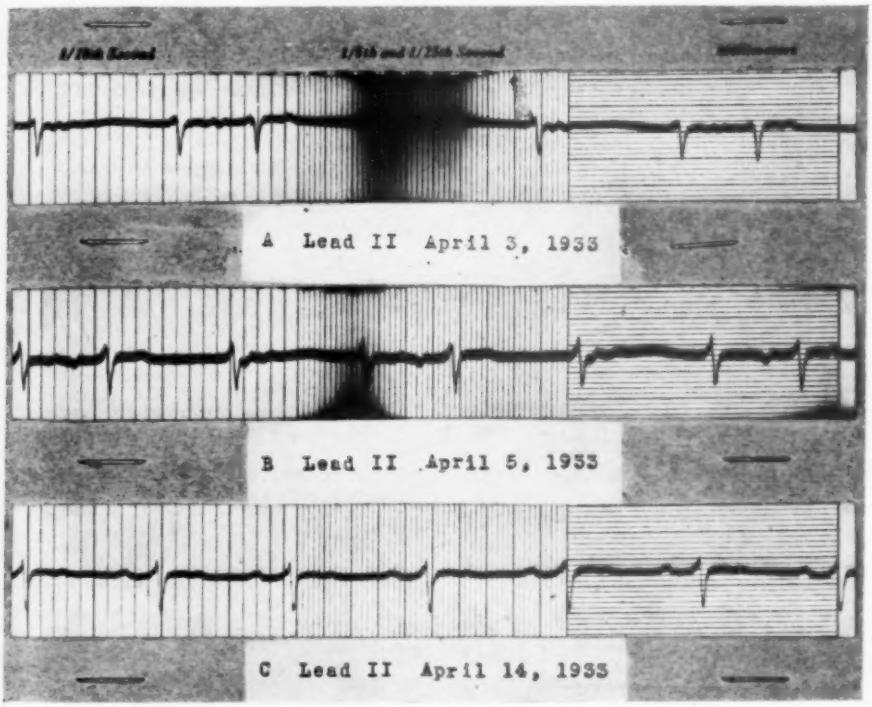

FIG. 2. Lead II only of electrocardiograms showing A–V dissociation and return to normal rhythm.

A. Taken April 3, 1933. Auricular rate 48, ventricular rate 66. P–R interval 0.28 sec. The auricles and ventricles are dissociated except periodically when an impulse from the more slowly beating auricle reaches the ventricle during a non-refractory period and causes a ventricular contraction. The P-waves are inverted showing a shift in the auricular pacemaker away from the sino-auricular node.

B. Taken April 5, 1933, one-half hour after the hypodermic administration of atropine sulphate grs. 1/100. Shows the same phenomena as (*A*) except that the ventricular rate is more rapid (80 per min.) and the P–R interval less prolonged (0.24 sec.).

C. Taken April 14, 1933. Regular rhythm, rate 60, P upright, P–R interval 0.28 sec.

sponse to the auricular impulse. This occurred when the impulse reached the ventricle during a phase in the cycle in which the muscle was not refractory from a previous contraction. The following day another electrocardiogram (figure 2 *B*), taken one-half hour after the hypodermic administration of atropine sulphate, grains 1/100, showed the same abnormal rhythm but with less prolongation of the P–R interval (0.24 sec.) and a more rapid ventricular rate (72 min.). The abnormal rhythm shown in these electrocardiograms is an example of the rare condition of auriculo-ventricular dissociation with unidirectional block and a more rapid ventricular rate such as has been reported by White [7] and Hewlett [8] in cases of digitalis poisoning. The drug was discontinued.

In spite of the development of this abnormal rhythm there was very marked clinical improvement. The symptoms of dyspnea, cardiac asthma and Cheyne-Stokes breathing were relieved. The pulse continued to be slow and usually irregular until April 6 when it became regular with a rate of from 60 to 80 per minute. The electrocardiogram taken on April 14 (figure 2 *C*) showed a return to normal rhythm with auricular and ventricular rates of 60, a P–R interval of 0.28 sec., and no change in the deflection of the various complexes.

The patient was discharged from the hospital on April 17 with no symptoms of circulatory failure. He was advised to remain in bed at home and to take digitalis leaves, gr. 1 twice daily. For the next two weeks he continued to feel well. At the end of that time his heart rate gradually began to increase. Coincident with this increase in heart rate the symptoms of nocturnal dyspnea, Cheyne-Stokes breathing and cardiac asthma returned.

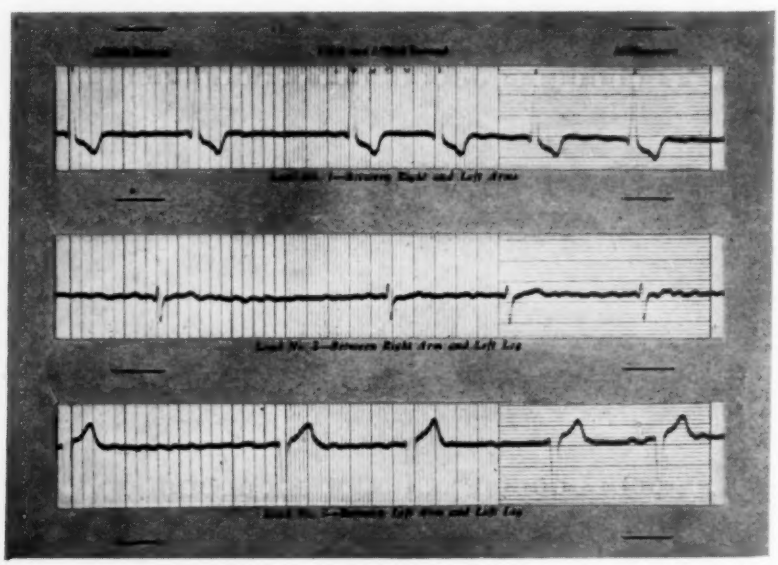

FIG. 3. Electrocardiogram taken July 15, 1933, showing auricular fibrillation with a ventricular rate of 40 to 50 per min.

He was readmitted to the hospital on May 9 with symptoms of advanced circulatory failure. Distention of the jugular veins, moderate cyanosis and very evident dyspnea were present. The heart rate was 110. Pulsus alternans was present with a systolic blood pressure of from 170 to 180 and a diastolic pressure of 110. Many moist râles were heard at the bases of the lungs. In addition to his previous symptoms he now presented the picture of a failing right ventricle with enlargement of the

liver and subcutaneous edema over the sacrum. Urinalysis showed a moderate cloud of albumin and many hyaline and granular casts.

The administration of powdered digitalis leaves, gr. 1 twice daily, was continued and a diuretic regimen instituted consisting of a low fluid intake, ammonium nitrate, grains 90 daily, and the intravenous injection of salyrgan, 1 c.c. at two- to three-day intervals. Under this regimen evidences of congestive failure disappeared in about two weeks' time. However, the subjective symptoms of dyspnea, especially at night, apprehension and occasional attacks of substernal oppression were relieved only partially.

During a period of two weeks his condition remained stationary except for slight recurrences of the congestive symptoms of liver enlargement and dependent edema which cleared up promptly following the administration of ammonium nitrate and salyrgan. The pulse rate remained slightly elevated, varying from 80 to 100 while at rest in bed. There was no significant change in the blood pressure readings.

On July 15, the pulse rate dropped to from 50 to 60 per minute and became irregular. An electrocardiogram (figure 3) showed that the irregularity was now due, not to A–V dissociation, but to auricular fibrillation with a very slow ventricular rate. Coincident with the development of the slow heart rate he began to improve rapidly and in a few days the dyspnea, Cheyne-Stokes breathing and cardiac asthma had disappeared. The administration of digitalis, which was discontinued with the drop in pulse rate, was resumed on July 22 with a dose of 1 1/2 grains daily, and the dose increased to two grains daily about 10 days later. Auricular fibrillation continued with a ventricular rate of from 60 to 70. The patient was allowed to be up for gradually increasing intervals and was discharged from the hospital on August 4 feeling quite well except for weakness and slight dyspnea upon exertion.

It has now been 21 months since he left the hospital. During this time his heart has continued to fibrillate. The ventricular rate has been maintained at from 50 to 60 per minute by the administration of 1 1/2 to 3 grains of powdered digitalis leaves daily. He has felt very well and has had no subjective symptoms of circulatory failure although his activities have been restricted only to a moderate degree.

Discussion

In the case reported, as often happens in the presence of a decompensating heart with a rapid regular sinus rhythm, digitalis administration resulted in very little if any slowing of the heart rate or improvement in the patient's general condition until the development of auriculo-ventricular dissociation with a slow ventricular rate. It was felt that digitalization had been pushed to the limit of tolerance and even intoxication prior to this as nausea and vomiting, necessitating withdrawal of the drug, had developed on two occasions.

The development of an abnormal rhythm was at first considered another unwelcome incident of digitalis intoxication. To our surprise, however, the patient became much more comfortable and began to show rapid improvement as soon as the slow rate developed. Within a period of two weeks his condition was satisfactory for dismissal from the hospital. After the abnormal rhythm had been present for three days the cardiac mechanism again became normal but with a slow rate, and his condition remained satisfactory for a period of two weeks. The rate then increased gradually to from 100 to 110 per minute in spite of continued bed rest and the administration of two grains of digitalis leaves daily. Coincident with the increase in the heart rate, symptoms of circulatory failure again appeared.

When he was admitted to the hospital the second time, moderately severe congestive failure had developed in addition to the marked symptoms of left ventricular failure. The congestive symptoms cleared up promptly following the administration of salyrgan and ammonium nitrate but recurred several times. His improvement was again unsatisfactory until the development of a very slow ventricular rate, this time due to auricular fibrillation with a high degree of auriculo-ventricular block.

Auricular fibrillation has continued for 21 months. The rate has been maintained at from 50 to 60 per minute by digitalis, and there has been no recurrence of circulatory failure although he has been engaging in moderate activity.

The improvement which followed the development of an abnormal rhythm with a slow ventricular rate upon the first occasion was considered a coincidence. A repetition of the experience upon the second occasion convinced us that the abnormal mechanism was really the means by which improvement was effected. The ventricular rate could then be slowed by digitalis and more efficient cardiac function obtained by the increased coronary blood flow and diastolic rest of the myocardium made possible by the longer period of diastole.

Conclusion

A case of circulatory failure in which improvement was twice dependent upon the development of an abnormal cardiac rhythm is reported.

Our experience in this case demonstrates the improvement in cardiac function which may result when an abnormal rhythm with a slow rate replaces a regular rhythm with a rapid rate. This improvement may be explained by the more effective depression of auriculo-ventricular conduction by digitalis in the presence of an abnormal mechanism such as auricular fibrillation.

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A REPORT OF IDENTICAL ALBINO TWINS OF NEGRO PARENTS*

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THE object of this report is to record identical twins and total albinism occurring in the Negro race. Although such an anomaly in identical twins is exceedingly rare in all races, we believe that the biologic phenomena involved in the production and accidental association of identical twins and albinism have been satisfactorily, if not correctly, explained in the literature on twins, twinning, and albinism. These children were neither pupils nor patients of ours; therefore, the only tests or examinations which could be made were those which are reported here.

The twins were girls, aged about eight and a half years (figure 1). Each weighed 20.9 kg., and was 131 cm. in height. They were well developed, well nourished, and appeared healthy. Their hair was abundant, snowy white, and coarse; when combed out, the hair of each child was equal in length. The degree of kinkiness of the hair; the distance between kinks; the hair line on the foreheads, about the ears, along the sides of the temples, and down the back of the necks were identical for each child. The skin, also, was totally devoid of pigment, and there were no freckles, moles, or blotches. The skin was fine and soft in texture; it was moist and delicate. It became sunburned from very short exposure, and required a great deal of protection during the summer months. (One of the children had a large, blistered sunburn on her back at the time of the examination.) The ears were small. The noses were flat, and the nares were wide apart. The lips were moderately thick, and the features were characteristically Negroid. The eyes were squinty, red and nystagmic. When the four eyes rolled from right to left, or vice versa, in order to follow the examining finger, all the nystagmic motions were synchronous. Examination of the ocular fundi revealed that the choroids were devoid of pigment. Examination of the ears, nose, throat, tonsils, thyroid gland, heart, lungs, abdomen, reflexes, and extremities of each child did not reveal anything unusual. After the children had reclined quietly on a bed for 20 minutes, the heart rate of each child was found to be 100 beats per minute. The value for the blood pressure of each child was 130 mm. of mercury for the systolic and 70 mm. of mercury for the diastolic. Their respirations were abdominal in type, and the respiratory rate was 20 per minute. The following measurements were obtained for each child: circumference of thorax, 55 cm.; circumference of neck, 28 cm.; circumference of waist, 55 cm.; circumference of middle third of thighs, 24 cm.; circumference of calves of legs, 20 cm.; circumference of middle third of arms, 16 cm.; circumference of wrists, 12 cm.; length from the fourth thoracic vertebrae to tips of fingers when arms were extended laterally, 70 cm.; length of legs from anterior-superior spine of ilium to soles of heels, 65 cm.; and length of the middle fingers from wrists, 14 cm.

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† Research Series, number 411.

These children had been born at term, after a short labor which had lasted four or five hours. The second child had been born about 10 or 15 minutes after the first. The mother was certain that there had been only one "after-

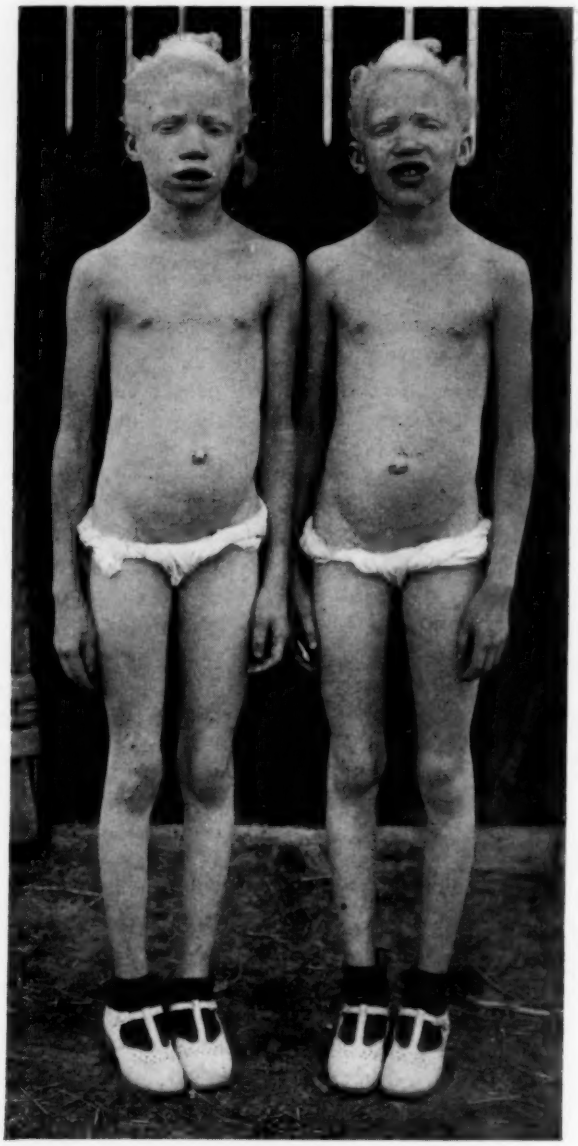

FIG. 1. The twins at the time they were examined.

birth." From birth, the children had been fed on the breast until they had been "two or three" years of age. The mother thought that one of the children always had been a little larger than the other. They had enjoyed good health. Their only illnesses had been measles and chickenpox, which had occurred simul-

taneously and had been of the same severity in each. It had been very noticeable that when one of the children had had a cold or any sort of illness, the other had been affected similarly and to the same degree. Their likes and dislikes of food and clothes were identical. They may have quarrels and disagreements between themselves; however, it is impossible for one of the family to disagree with one of the twins without invoking the anger of the other.

Mental tests under our supervision probably would not have been of much value. These children were quiet, modest, polite and obedient. They had never had an opportunity to go to school. It is our opinion that they were mentally within normal limits.

FIG. 2. The maternal grandmother, the mother, the twins, and two of their cousins (girls), two years prior to examination.

In neither the father's family nor the mother's family (figure 2) were albinos or admixture of the white race known to be present. The father appeared to be full-blooded Negro. We saw the mother's parents, who, like the mother, were moderately black, and had the characteristic skin, features, and hair of Negroes. The possibility of admixture with the white race or any other race is admitted. This we believe to be irrelevant because albinism and identical twins occur in all races.

COMMENT

The essential feature of albinism is the total absence of pigments of the melanin group, which are the chief factor in the surface coloration among all animals. The absence of these pigments in the eye results in the primary incapacitation of this affliction. The ordinary causes of pigmentation, whatever they may be, are not operative in the albino. Short exposure of albinos to hot sunlight produces a hyperemia which very quickly is followed by the formation of blebs if the exposure is continued. The fat and blood pigments are normal and are excreted in normal quantities in the urine; whereas, the mechanisms for

metabolism and control of the pigments of the melanin group are nonoperative. The foregoing statements apply only to genuine albinism, which is not the most common form observed. In cases of incomplete albinism, the hair has various tints from yellow to red. The usual albinic Negro has yellow hair and pigmented freckles.

There is still a third type which is termed partial albinism. These individuals may have albinic eyes, or they may have albinic skin, normal eyes, white locks of hair. In the latter case, the skin may be flecked with white, and there may be piebald skin or the so-called mosaic inheritance. Clinically, partial albinism should be distinguished from such conditions as vitiligo.

In the majority of instances, albinism continues throughout life. However, it has been stated that an individual who had been born albinic occasionally has recovered. Apropos of this, mention should be made of the seasonal albinism in Arctic mammals and birds. As far south as Minnesota, during winters with much snow, the jackrabbits (subgenus Macrotolagus) become albinic.

By selective breeding, albinism can be reproduced indefinitely among lower animals. Thus, the mode of incidence of this inborn error would seem to have a ready explanation, if it is regarded as a rare recessive character in the mendelian sense. If two characters, one of which tends to be dominant, and the other, recessive, are observed in cross-bred individuals, the dominant character will tend to be manifested. This manifestation of the dominant character is explained by the supposition that the germinal cells or gametes of each generation are pure so far as the qualities in question are concerned. It is by such reasoning that Mendel's theory accounts for the numerical results observed by the production of dominant and recessive gametes in equal numbers in successive generations of inbred individuals in the less complicated gametes. The length of life of man, his limited reproductive capacity, his innate tendency to forget unpleasant details in the family history, and especially those matings and the resulting offspring which may be considered undesirable and, finally, his qualities of nomadism, and infidelity, render mendelian interpretation of his dominant and recessive characters practically impossible. Thus, the occurrence of such an inborn error as albinism among human beings is in reality an accidental fertilization of an ovum, which possesses recessive pigmentary characteristics, by a similar spermatozoön, except in consanguineous marriages. To illustrate the results of consanguineous marriages, in 24 families which contained 60 albinic members, five of these latter were the offspring of matings of first cousins. In only two instances was albinism directly transmitted from parent to child.

The reports of genuine identical albinic twins are scarce. According to Garrod,[1] there are 29 records of twins, one or more of whom were albinic. In 11 pairs, both were albinos and in 18 pairs, one twin was normal. In 20 cases the twins were of the same sex, and in seven cases they were of different sexes; the sex of two pairs was not stated. In 10 cases in which both twins were albinic, both of the twins were of the same sex. Since it usually has been argued that identical twins are always of the same sex, probably no more than 10 pairs of these twins were identical. Furthermore, the probabilities are that all of these 10 pairs were not identical twins.

The biology of twins [2] and the physiology of twinning [3] among human beings has been considered in great detail by Newman and his associates. They ex-

pressed the opinion that a single ovum, or identical twins are the result of one of the following processes: (1) fission of the blastoderm, (2) double gastrulation, or (3) fission of the bilateral halves of a single embryonic axis. In order for any one of these processes to take place, some retarding mechanism must be present, which prevents normal implantation of the fertilized ovum. One of the following possibilities probably is the retarding mechanism: (1) a defective development in the stimulating mechanism of the spermatozoön, (2) a defective stimulating influence of the corpus luteum on the uterine mucosa, or (3) twinning, which is an hereditary character dependent on a recessive gene.

It is interesting that, in a consideration of identical twins who are also albinos, the possibility of both the occurrence of the twins and the albinism may have genetically similar origins. That is, both may be the result of opportunely placed recessive genes so that in the formation of the gamete the conditions are there for both anomalies.

Summary

Identical albinic Negro twins have been described. Some of the essential features of albinism and twinning have been discussed. Whatever the fundamental mechanisms are for the production of albinism and twinning, they are present in the original germ plasm. The scarcity of the combination of genuine albinism in identical twins, as indicated by the literature, has been pointed out.

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EDITORIAL

FACTORS IN THE FALLING DEATH RATE FROM TUBERCULOSIS

For fifty years the tuberculosis death rate has shown a striking and fairly steady decrease, so that in the United States it is now about one-sixth of its height in the eighties. Moreover, this remarkable phenomenon has been observed to a greater or lesser extent in most of the European nations. On the other hand a world survey indicates that there are still countries, such as Puerto Rico and the Philippines, in which the mortality from tuberculosis not only stands at a very high level but appears to be actually rising.

The recent studies [1, 2, 3, 4] bearing on the causes of these variations have by no means completely clarified the problem, but they have at least broadened our conception of the epidemiology of the disease and incited the collection of more accurate data which will perhaps in time make it possible to substantiate what is at present to a considerable extent surmise.

Certain environmental factors, such as urban or rural residence, type of housing, food supplies, occupation, wages, etc., have long been known to show a correlation with the tuberculosis death rate in groups better or worse situated in these regards. That these are potent factors in increasing the incidence of infection with tuberculosis in a community and in activating latent infections is scarcely disputable. Indeed, under the strain of the extreme conditions of malnutrition, crowding, overwork and exposure engendered by the World War, the death rate from tuberculosis in the chief combatant nations rose abruptly during the war years. When, however, one considers the fifty years from 1883 to 1933 in this country, during which the fall in death rate from this disease from approximately 360 to 60 per 100,000 has occurred, it is apparent from the details available that no change in purely environmental factors is sufficient to explain what has occurred. The rate has fallen in urban as well as in rural communities during this period, it has fallen in spite of a tremendous influx of country dwellers into the cities, it has fallen even in the crowded slums, even in the more dangerous occupations, and it began its fall in a period of low wages and unemployment and has continued to fall through several panics and notably through the recent unexampled depression. It seems evident that some more fundamental cause exists for the regression of tuberculosis than variations in purely environmental factors.

[1] Flatzeck-Hofbauer, Alfred: Kommen und Gehen der Tuberkulose, Curt Kabitsch, Leipzig, 1931, p. 102.

[2] Long, Esmond R.: The rise and fall of tuberculosis in certain American peoples, Puerto Rico Jr. Publ. Health and Trop. Med., 1935, x, 270–287.

[3] Drolet, Godias J.: Epidemiology of tuberculosis; in Goldberg's Clinical Tuberculosis, Vol. I, p. A3–A61. F. A. Davis Co., Philadelphia, 1935.

[4] Whitney, Jessamine S.: New and supplementary facts and figures about tuberculosis, National Tuberculosis Association, New York, 1935.

It might be assumed that, following the discovery of the contagiousness of tuberculosis in 1865 and the isolation of the tubercle bacillus in 1882, the consequent gradual development of a great international campaign against this disease was the potent factor leading to its increasing control. The history of this movement, however, shows that it was merely in its infancy during the first twenty-five years of the falling tuberculosis death rate. Even today when there are estimated to be 73,000 beds for tuberculous patients in the United States and over 8,000 public health nurses devoting some of their efforts to the campaign against this disease, it is probably true that anti-tuberculosis measures are not the underlying cause of the continuing subsidence of the disease, though they undoubtedly constitute our most effective method of hastening its decrease in our communities. The difficulties of control measures are better realized when it is stated that there are probably between four and five hundred thousand cases of clinically active tuberculosis in the United States and that the relatively scant data available as to the incidence of infection in the total population would suggest that over 50 per cent have been attacked.

In recent times there is a growing tendency among students of this disease to pay more heed than formerly to the development of racial resistance as possibly the chief factor in its diminution as a cause of death. According to this conception the last fifty years in this country constitute a waning phase of a long drawn out epidemic of tuberculosis.

The word epidemic used in this connection may sound a little strangely and yet there exist a number of reported instances which illustrate clearly the possibility of relatively brief and acute epidemics of tuberculosis. Among the Canadian Indians placed in the Qu' Appelle reservation about 1880 the disease became epidemic about 1884. By 1890 the mortality rate had reached a height of 9,000 per 100,000. It then began to fall relatively rapidly and reached 1,000 per 100,000 in 1907. It remained at close to this level until 1926 and then fell rapidly to 273 per 100,000 in 1931. During the height of the epidemic an acute generalized form of the disease predominated; as the epidemic subsided the dominant type was a chronic one. The incidence of glandular involvement in the population was estimated at 33 per cent in the '90's, whereas in 1932 less than 1 per cent of the school children were found to have this malady. This outbreak as recorded by Ferguson [5] is a classical example of the epidemic characteristics of tuberculosis in a susceptible race. There are excellent records also of the wave-like spread of tuberculosis in the Scandinavian countries from the cities in the south where it raged in the last century to the sparsely settled northern regions where the highest rates are now observed.

In support also of the influence of human resistance in altering the epidemic characteristics of tuberculosis may be cited the known differences in racial and national resistance to tuberculosis as observed in some of the

[5] FERGUSON, R. G.: The Indian tuberculosis problem and some preventive measures, Trans. 29th Annual Meeting Nat. Tuberc. Assoc., 1933.

larger cities of this country. Throughout the country the tuberculosis mortality among Negroes is very much higher than among whites; in 1932 in the registration area the rate for whites was 49.7 and for colored was 171.9. That this higher rate cannot be due merely to greater opportunity for infection is indicated by the fact that tuberculin testing in childhood in New York does not show any higher incidence of infection among the colored than among the white children; the difference in mortality rates in these races in this city (white, 52; colored, 260) must depend, therefore, on the difference in ability to combat the infection after it has been acquired. This is borne out by the suggestive studies of Asserson [6] who found in testing babies of different national origins that all were infected at practically the same rate, but that when the positive reactors were later followed up 8 per cent of the Irish babies had died, 5 per cent of the Italian, 3.5 per cent of the American and 1.2 per cent of the Jewish.

The importance of this factor of racial resistance is again indicated by the repeated observations which show that in races with low resistance and high mortality rates there is a preponderance of deaths in infancy and the preadult years, a high occurrence of rapidly generalizing forms, of massive exudative lesions and of lymph gland involvement; whereas in nationalities in which the tuberculosis mortality has fallen to a low level there is a great decrease in mortality from the disease in infancy, the peak of the death rates occurs in those over 40 years of age and the characteristic pathologic changes of the disease are chronic localized fibrotic lesions in the lungs. It seems that by a study of the age incidence of the deaths, the frequency of the various clinical forms and the distribution and character of the pathologic lesions one might assess the progress made by any racial strain towards effective resistance to the disease.

It is too early to do more than speculate about the character of this resistance to the extension of tuberculous infection. There are two facts, however, which seem self evident. At the stage of a tuberculosis epidemic where the greatest number of deaths occurs in infancy and childhood, the nation involved is being subjected to a drastic process of selection whereby only the more resistant survive long enough to propagate the race. In the second place no degree of resistance has yet been developed which in the face of exposure to the disease will keep down to very low levels the incidence of infection.

Analysis of the statistics of tuberculosis in the United States suggest that national resistance to the disease is growing steadily higher. If the death rate continues to fall the number of active cases will eventually shrink to manageable proportions. In this phase control measures may deal the decisive blow.

It would not do to close upon this optimistic note without in fairness pointing to the reverse of the shield. There is every reason to believe that a population in which there is very little tuberculosis becomes in time a

[6] Asserson, M. A.: Tuberculosis in infants, Am. Rev. Tuberc., 1927, xvi.

population highly susceptible to rapidly fatal forms of the disease. It has already been noted that there is an increasingly high proportion of tuberculin negative young adults in the entering classes of our schools. These must be looked upon as a large group of persons who have escaped exposure to infection. The interesting observation has been made in certain training schools for nurses that it is in this tuberculin negative group that the majority of the active clinical cases of tuberculosis develop. This may indicate that we are already beginning to develop a group of people in this country who survive not by virtue of resistance to tuberculous infection, but by grace of fortuitous lack of exposure.

We may conclude that unless it prove feasible to completely exterminate tuberculosis we shall be saved from recurring epidemics due to loss of racial resistance only by the discovery of some immunizing agent.

REVIEWS

Behavior Development in Infants; a Survey of the Literature on Pre-Natal and Post-Natal Activity, 1920–1934. By EVELYN DEWEY, New York, published for the Josiah Macy, Jr., Foundation, by Columbia University Press.

This book deals primarily with literature which has accrued since 1920 covering the fetal period and the first two years of life. The references are confined to the theories drawn from psychology and biology on the fundamental processes underlying growth and development of behavior, and to objective studies of fetal and infant behavior.

The material is organized as follows: Part I, growth processes—theories of behavior development, evidence from biology and neurology, correlation of structure and function from animal studies; Part II, behavior of the human fetus; Part III, neonatal behavior; Part IV, behavior during infancy; Part V, summary and conclusions. A bibliography of 216 titles is included.

The writer has avoided mere citations and direct quotations from the various authors and has instead attempted to assimilate and interpret the mass of ideas which has gathered around the development of certain types of infant behavior. The individual abstracts are extremely well written and the entire book is so organized as to provide continuity of thought, which makes for sustained interest and readability.

The literature surveyed covers a period during which there has been great progress in technic of research in infant behavior. The book is an invaluable reference handbook for those who are interested in the problems covered, including not only physicians, but psychologists and biologists as well.

A. J. R.

Practical Neurological Diagnosis, with Special Reference to the Problems of Neurosurgery. By R. GLEN SPURLING. xi + 233 pages, with 99 illustrations. Charles C. Thomas, Springfield, Illinois. 1935. Price, $4.00.

Anyone who has had the task of presenting clinical neurology to undergraduate students will appreciate the motive which led the author to compile "a simple account of the principles of neurological diagnosis." The method of presentation of the subject in teaching, as well as in such a treatise, is always a matter of concern. What shall be stressed and what shall be omitted? Is it better to "cover the field" and leave the average student with a hodge-podge memory of neurology, or present the kernel of elementary neurology so that he at least can recognize the common disorders of the nervous system?

The author has chosen to present the basic facts which he feels will give the student a working knowledge. The book is divided into three parts: neurological examination, cerebrospinal fluid, and x-ray diagnosis. The first part consists of seven chapters in which the chief subdivisions of the nervous system are covered. The opening chapter deals with the patient's history and gives several important points in history-taking. A little more detail here would have been advantageous. A well-taken neurological history will often tell the practitioner that something is wrong with the nervous system when an examination alone might fail. The cranial nerves are taken up in order. There is a brief anatomical review for each with the clinical application and the technic of examination. This section is very well done. The cerebrum and cerebellum are similarly presented in Chapters 3 and 4. A text written by a neurosurgeon would naturally devote considerable space to these subdivisions because of the great importance of cerebral localization in neurosurgery. However,

it seems that 14 pages devoted to the frontal lobe is a little out of proportion to the brevity used elsewhere, especially when one realizes that the physiology of this lobe still presents many unanswered questions. Only proved clinical facts would seem to have a place in an outline of this type. The examination of the motor and sensory systems is discussed in the chapter on the spinal cord. The presentation here seems a bit disjointed and lacking in perspective. The chapter dealing with reflexes is very well done.

The section on the cerebrospinal fluid is clear and concise. The technic of lumbar puncture, the examination of the fluid, and cerebrospinal fluid dynamics are discussed.

The final chapter deals with roentgen-ray diagnosis, including routine skull examinations, air injections, and lipiodol technic.

The book is up to the usual quality of this publisher. It is well illustrated with 99 well-chosen diagrams and photographs. The bibliography contains 18 titles. Students will find this book of interest.

J. G. A., Jr.

Around a World on Fire. By Karl E. Kassowitz. 198 pages; 14 × 19.5 cm. Gutenberg Publishing Company. 1935. Price, $2.00.

The World-War gave rise to many strange and thrilling journeys, only a few of which have been printed. The story of Dr. Kassowitz's experiences as an Austrian army surgeon attached to combatant troops, his capture by the Russians and removal to Siberia, his escape with a comrade and flight in Chinese disguise across the frozen wilderness of North China to the relative safety of the Austrian Legation in Pekin and his eventual return to Austria after imprisonment by the British at Gibraltar,—all this high adventure is told vividly and modestly and almost too briefly in this attractive little volume.

M. C. P.

Diagnosis and Treatment of Disorders of Metabolism. By James S. McLester, M.D. 328 pages; 24 × 15.5 cm. Oxford University Press, New York. 1935.

This book reflects the conventional viewpoint concerning metabolic disorders as understood and written about a decade or two ago. The subjects treated include gout, obesity, diabetes, and disorders of the intermediary metabolism, which embrace uraturia, oxaluria, phosphaturia, cystinuria, alkaptonuria, hemochromatosis and pentosuria. Aside from diabetes there is no mention of other endocrine diseases or any hint that these also are important disorders of metabolism. There is nothing about disturbances of calcium metabolism, or of thyroid dysfunction, although basal metabolism is mentioned. If obesity is discussed, it would seem necessary to treat of undernutrition also. The chapter on disturbances of the water balance is highly inadequate. That on acidosis contains directions for various chemical determinations for which the reader might better be referred to one of the standard laboratory manuals. Some of the directions for determination of the plasma carbon dioxide capacity, for the determination of its hydrogen-ion concentration and for estimation of the alveolar carbon dioxide tension, are obsolescent, and indicate lack of recent familiarity with the procedures.

Altogether this is not a very adequate book and cannot be conscientiously recommended.

G. A. H.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D. (Berlin). 492 pages; 25 × 18 cm. William Wood and Company, Baltimore. 1935. Price, $11.00.

The author is one of the several eminent internists lost temporarily, at least, to Germany by reason of the political upheavals of the past few years. He is a member of a family prominent in medical science. His brother's name linked with that of Aschheim is widely known in connection with a test for pregnancy. The author's reception in England where he worked for some time in Manchester before going to Palestine doubtless led to this revision of the 1926 German edition of his work and to the excellent translation by Prausnitz.

"Primarily a book for the clinician," it is admirably adapted to this purpose. The first or general part occupies 105 pages of this nearly 500 page volume and contains eleven chapters including those on the relations between the different glands, the physiology and chemistry of the hormonal glands, hormones and vitamins, the vegetative nervous system and its relations to the hormonal system, methods for the examination of patients and general remarks on organotherapy.

It is in the second or special part comprising four-fifths of the volume that the unusual arrangement will appeal particularly to the clinician. Here are considered definite clinical pictures, e.g., Graves' disease, myxedema, tetany, obesity, diencephalopathy, acromegaly, dwarfism, osteomalacia, osteitis fibrosa, Addison's disease, diseases of the generative system and others. The subjects are presented as problems in internal medicine and the glandular and hormonal factors are fully discussed. Case reports and illustrations are taken from the author's own patients.

His points of view as a rule are logical and conservative. To quote a paragraph from the preface, "A number of fundamental hypotheses, some of which were derived from the author's personal work on the hormone problem, run through the book and give it its special outlook. As instances the following may be cited: (1) Hormone effect is not an absolute but a variable quantity, depending not least upon the momentary condition of the organ on which it acts, more especially the physicochemical conditions of its cells, (2) Functional and anatomical changes in endocrine glands should not always be regarded as the cause of disease, but in many cases as the reactions of the glands to morbid processes primarily located in certain other organs, (3) With phylogenetic evolution and progressive differentiation of cellular functions, the hormone appears on the scene as the intensifier of such functions; even in the most highly developed beings, however, not all of them are indispensable to life, (4) The endocrine system is but one link in the chain of vegetative functions of the organism. This should be emphasized in order to avoid the danger of overestimating the rôle of the hormonal factors."

The book may be highly recommended to the clinician for whom it was prepared.

T. P. S.

Practical Endocrinology. Symptoms and Treatment. By MAX A. GOLDZIEHER, M.D. 358 pages; 22 × 15.5 cm. D. Appleton-Century Company, New York City. 1935. Price, $5.00.

The author is entitled Endocrinologist, Gouverneur Hospital; Chief of Endocrine Clinic, Gouverneur and Brooklyn Woman's Hospitals; former Professor of Pathology, Royal Hungarian University, Budapest. He has been an active worker in this field for many years and is the author of another book, "The Adrenals."

"Practical Endocrinology" is quite a readable book; it is divided into short chapters and is expressed in a simple and direct style. The arrangement of subject matter is pleasing to the reviewer but may quite possibly offend other readers. There are three short introductory chapters on morphology and physiology of the endocrine

glands and on the examination of the patient. Following sections relate to Disturbances of Development and Growth, Disturbances of Nutrition, Disturbances of Metabolism, etc., with, in closing, a brief and succinct section on treatment. The reader must use the index and turn many leaves to get the full picture of a definite disease, e.g. Graves' disease or myxedema.

The author seems a sufficiently ardent therapeutist, somewhat conservative toward surgery and x-ray treatments but leaning rather heavily on organotherapy. He recommends pituitary and adrenal tablets by mouth in addition to similar products parenterally. He also describes methods of physical therapy, diathermy and light treatment, adapted to the endocrine organs.

The book was written and arranged for the general practitioner. It expresses the ideas and opinions of the author without argument or discussion. There are no references to the work of others. It is not therefore a good work for students if their skepticism is to be stimulated by differences of opinion: but the book will doubtless be highly valued by those who know the author well and who have great confidence in his opinion.

T. P. S.

COLLEGE NEWS NOTES

New Life Members

The total number of Life Members in the American College of Physicians has been increased to fifty-eight. The following Fellows have become Life Members since January 1, 1936, their listings being in the order of their accession:

Dr. Casper H. Benson, Columbus, Ohio
Dr. Donald Gregg, Wellesley, Mass.
Dr. James Ray Arneill, Denver, Colo.
Dr. Thomas Fitz-Hugh, Jr., Philadelphia, Pa.
Dr. C. Charles Burlingame, Hartford, Conn.
Dr. Noble Wiley Jones, Portland, Ore.
Dr. Cecil M. Jack, Decatur, Ill.
Dr. Roy M. Van Wart (formerly of New Orleans, La.), Descanso, Calif.

The members of the Board of Regents of the College have joined in issuing a personal invitation to the Governors to a dinner to be held in Detroit on Sunday evening, March 1, prior to the opening of the Clinical Session.

State Meeting of College Members in Louisiana

Under the Chairmanship of Dr. Joseph E. Knighton, Governor of the College for Louisiana, a combined scientific and social meeting was held at Shreveport on January 30, 1936. The meeting was conducted particularly for those Fellows and Associates of the College residing in and about Shreveport, and was attended by some guests, one of whom was the President of the local organization representing the American College of Surgeons.

Dr. T. P. Lloyd discussed subacute bacterial endocarditis, with a report of a case; Dr. W. S. Kerlin discussed pernicious anemia and exhibited a patient showing the characteristic achylia and neurological changes, but only minor blood changes; Dr. A. A. Herold discussed recent developments in the treatment of diabetes.

The scientific discussions were followed by a dinner and a delightful evening of good fellowship. Similar meetings are planned for the future.

Gifts to the College Library

Acknowledgment is made of the following gifts to the College Library of publications by members. Special emphasis is placed on gifts of books of which members are the authors, for the College is desirous of obtaining particularly all books written by its members.

Dr. Sigmund S. Greenbaum (Fellow), Philadelphia, Pa.—one autographed book, "Diseases of the Mouth and Their Treatment."

Dr. J. Arthur Myers (Fellow), Minneapolis, Minn.—two books, "Modern Aspects of Diagnosis, Classification and Treatment of Tuberculosis" and "The Child and the Tuberculosis Problem."

Dr. Linn J. Boyd (Fellow), New York, N. Y.—one translation, August Bier's Study on Inflammation.

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa—one reprint, "The Social Security Act."
Dr. Herbert T. Kelly (Fellow), Philadelphia, Pa.—one reprint.
Dr. Alfred J. Scott, Jr. (Fellow), Los Angeles, Calif.—one reprint.
Dr. John W. Torbett (Fellow), Marlin, Texas—two reprints.
Dr. Stephen H. Curtis (Associate), Troy, N. Y.—six reprints.
Dr. William B. Grayson (Associate), Little Rock, Ark.—two reprints.
Dr. R. R. Hendershott (Associate), Tiffin, Ohio—one reprint.

At the Fourth Annual Symposium on Heart Disease of the Los Angeles County Heart Association, during December, the following Fellows contributed as indicated:

Dr. John C. Ruddock—"Coronary Occlusion."
Dr. B. O. Raulston—"Circulatory Edema."
Dr. E. Richmond Ware—"Pulmonary Embolism."
Dr. R. Manning Clarke—"Paroxysmal Tachycardia."
Dr. A. M. Hoffman—"Peripheral Vascular Failure."
Dr. Donald J. Frick—"The Use of Drugs in Cardiovascular Disease."
Dr. A. S. Granger—"Diet in Heart Disease."
Dr. Howard F. West—"The Challenge of Arteriosclerosis."

The Guilford County Medical Society recently awarded to Dr. Frederick R. Taylor, High Point, N. C. (Fellow), a plaque for the most "outstanding contribution" to medical literature contributed by members of the society during the past year. Prominent among Dr. Taylor's contributions was a chapter in Oxford Medicine on "Arachnidism—The Clinical Effects of Spider Bite."

Dr. Mary O'Malley (Fellow), for many years Clinical Director of St. Elizabeths Hospital, Washington, D. C., has resigned that position and retired from active practice. She is now residing in Buffalo, N. Y.

Dr. Salvatore Lojacono (Fellow) has resigned the Superintendency of Morgan Heights Sanatorium at Marquette, Mich., effective January 25, 1936, and is now located in Lansing.

Dr. Walter P. Gardner (Fellow) has resigned from the Hastings State Asylum at Hastings, Minn., to accept the Medical Directorship of the Fergus Falls State Hospital at Fergus Falls, Minn. This is a two thousand bed hospital for psychiatric cases.

Dr. Edward Weiss (Fellow), a member of the Department of Medicine of the Temple University Medical School, has been made Professor of Clinical Medicine in that Institution.

Dr. Constantine P. Faller (Associate), Harrisburg, Pa., has been awarded the biennial Seibert Prize of $500.00 for study in Europe of the Harrisburg Academy of Medicine.

Dr. Joseph I. Linde (Fellow), Clinical Professor of Pediatrics, Yale University School of Medicine, is the Health Officer of New Haven.

Dr. Edwin C. Swift (Fellow), Jacksonville, Fla., is the President of the Florida East Coast Medical Association for the present year.

Dr. Arthur U. Desjardins (Fellow), Rochester, Minn., and Dr. Walter M. Simpson (Fellow), Dayton, Ohio, are members of the American Committee for the International Conference on Fever Therapy to be held in New York City during September, 1936. Therapeutic, physiologic and pathologic phases of fever will be discussed. All papers presented will be translated in abstract form into French, English and German.

Dr. Thomas F. Sellers (Associate), Atlanta, Ga., is Secretary of the newly organized Georgia Association of Pathologists.

Dr. William Henry Walsh (Fellow), Chicago, has been appointed as a consultant to study the hospital needs of the Institute of Tropical Medicine at San Juan, Puerto Rico.

Dr. Robert A. Black (Fellow), Chicago, has been appointed a member of the Chicago Board of Health.

Dr. Reginald Fitz (Fellow), Boston, Mass., for many years Associate Professor of Medicine at Harvard University Medical School, has been appointed Professor of Medicine in the Boston University School of Medicine and Director of the Robert Dawson Evans Memorial, the department of research and preventive medicine of the Massachusetts Memorial Hospitals.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., delivered addresses during the past year before the Congress on Gout and Uric Acid at Vittel, France, the International Congress of the History of Medicine at Madrid, Spain, and before the Pazmany Peter Royal University of Budapest.

Dr. Lewis J. Moorman (Fellow), Oklahoma City, was recently named to Oklahoma's Hall of Fame by the Oklahoma Memorial Association in recognition of his achievements in medicine. Dr. Moorman is a former Dean of the University of Oklahoma School of Medicine and ex-President of the Oklahoma State Medical Association and an ex-President of the Southern Medical Association.

Dr. Alvan L. Barach (Fellow), Columbia University College of Physicians and Surgeons, New York City, has received a grant from the National Research Council for research in the therapeutic use of helium.

Dr. Raymond G. Taylor (Fellow), Los Angeles, was elected one of the Vice Presidents of the Radiological Society of North America at its last annual meeting.

Dr. Frank H. Redwood (Fellow), Norfolk, Va., was elected a Vice President of the Seaboard Medical Association at its last annual meeting.

Dr. John G. FitzGerald (Fellow), Dean of the Faculty of Medicine and Director of the School of Hygiene and Connaught Laboratories, University of Toronto, delivered the annual Morris Hertzstein lectures, March 2–4, under the auspices of the Medical Schools of Stanford University and the University of California.

Dr. Millard E. Winchester (Fellow), Brunswick, Ga., has been reëlected Secretary of the Georgia Public Health Association for 1936.

Dr. Herbert A. Burns (Fellow), Superintendent of the Minnesota State Sanatorium for Consumptives at Ah-Gwah-Ching, has also been placed in charge of a new annex erected exclusively for treatment of Indians. The Indian annex will be under the direction of the State Board of Control, in coöperation with the Federal Office of Indian Affairs. It is said to be the first sanatorium in the United States for Indians, excepting a small inadequate one at Onigun on Leech Lake, which has now been destroyed by fire and the patients transferred to the new institution.

Dr. Anthony Bassler (Fellow), New York City, was elected President of the National Society for the Advancement of Gastro-Enterology at its annual meeting in New York during December.

Dr. Elliott P. Joslin (Fellow), Boston, Mass., delivered the Eastman Memorial Lecture, January 10, on "Diabetes of Today and Tomorrow," in connection with the tenth anniversary of the opening of the University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital and the School of Nursing.

CHARLES GODWIN JENNINGS, M.D., F.A.C.P.

OBITUARIES

CHARLES GODWIN JENNINGS

Charles Godwin Jennings was born at Leroy, New York, February 4, 1857, of the union of Thomas A. Jennings and Matilda Godwin. He began his education in the public schools of Seneca Falls, New York, and graduated in 1875 from Mynderse Academy. In the same year he began the study of medicine in a preceptor's office, where he remained until October 1876, when he entered Detroit Medical College from which he graduated, with the degree of Doctor of Medicine, in 1879.

During his Senior year he served as undergraduate interne in St. Luke's Hospital and upon graduation received the appointment of Resident Physician. In May 1880 Dr. Jennings began the practice of medicine in Detroit as Assistant to Dr. E. L. Shurley. Thus it is that Dr. Jennings practiced his profession in the city of his adoption continuously for fifty-six years. No truer estimate of the quality and scope of that long period of beneficent service to the public and his profession can be noted than the erection in 1930 of the Charles Godwin Jennings Hospital on Jefferson Avenue, largely by devoted friends and patients as an enduring testimonial of the appreciation, admiration and affection in which he was held by those who knew him best.

At one time or another he had held commanding positions on the staffs of all the Hospitals of his city. At the time of his death, Dr. Jennings was Chairman of the Board of Trustees and of the Medical Board and attending physician of the Charles Godwin Jennings Hospital. He was consulting physician to the Harper Hospital, the Grosse Pointe Hospital, the Children's Free Hospital, the Detroit Tuberculosis Sanitarium, and to the U. S. Marine Hospital.

In the period between 1881 and 1920 Dr. Jennings was a member of the Faculties of the Detroit Medical College and the Detroit College of Medicine and Surgery. Beginning his teaching as Lecturer in Chemistry he successively occupied the chairs of Professor of Chemistry, Professor of Diseases of Children, Professor of Practice of Medicine and Diseases of Children and finally Professor of Medicine. Dr. Jennings was a member of many medical societies and associations, among which are the American Medical Association, American Climatological Association, American Therapeutic Society, American Pediatric Society, The Michigan State and Wayne County Medical Societies and the American College of Physicians, in which he took an active part during the twenty years of his membership, having been Vice-President, Regent and Chairman of the Board of Governors. At the time of his death Dr. Jennings was Chairman of the Committee on Arrangements for the Annual Meeting in Detroit this year.

Dr. Jennings was 1st Lieut., Medical Reserve Corps, U. S. Army, 1911 to 1917; Captain, Medical Corps, U. S. Army, 1917–1919; on duty Camp Grant; member Central Examining Board at Detroit 1911–1918.

He had been a member and President of the Detroit Board of Health, member of Gorgas Memorial Institute, etc.

The University of Michigan conferred upon him the honorary degree of Master of Arts and from the College of the City of Detroit he received the honorary degree of Doctor of Science.

Dr. Jennings was a prolific reader. He was Associate Editor of the *Annals of Clinical Medicine* and of the *Archives of Pediatrics;* Editor of *The Microscope,* 1885–1890; contributor to Tice's Practice of Medicine, Therapeusis of Internal Diseases, and to the Cyclopedia of Diseases of Children.

Dr. Jennings was a member of the Yondotega, the Wilenagemota and the Grosse Pointe Clubs, as well as the Sons of the American Revolution.

It is not for his professional, scientific, literary or civic attainments, however outstanding, that Dr. Charles Godwin Jennings will be remembered by his colleagues far and near, but for the qualities of heart and mind, and the gift of true friendship possessed to the highest degree by this kindly gentleman. His charming personality, his keen sense of humor and his generous devotion to his friends, his colleagues and his students, won for him the confidence and affection of men and women throughout the United States and Canada. As evidence of the esteem in which he was held in his own State a testimonial dinner was given him on February 28, 1934, by the Wayne County Medical Society, on the fifty-fifth anniversary of his graduation in medicine. This dinner was attended not only by men prominent in medicine, dentistry and the civic leaders of the State, but also by colleagues from all parts of the country.

One of the underlying causes for Dr. Jennings' continued physical fitness, his alertness of mind and his unquenchable enthusiasm for his profession and for life in general was his devotion to his hobbies, namely fly-fishing and hunting, in each of which he was an expert. Each year saw him off to the great open spaces for several weeks with rod and gun.

Fortunate indeed were those of his close friends who were able to accompany this ardent sportsman and nature lover.

Few men, who have gone on the long journey, from any walk in life, are missed so acutely by as large a circle of loyal and devoted friends as is this great physician.

WILLIAM GERRY MORGAN, F.A.C.P.

DR. HENRY WALD BETTMANN

Dr. Henry Wald Bettmann (Fellow), Cincinnati, died December 5, 1935; aged, 67 years.

Dr. Bettmann was born in Cincinnati, attended public schools in that city, and graduated with highest honors at the University of Cincinnati. He was a charter member of the Cincinnati Chapter of Phi Beta Kappa. During his undergraduate days at the University he was a prominent member of the football team. In 1889 he graduated with high honors from the Medical College of Ohio (University of Cincinnati). After serving his interneship at the Cincinnati Hospital, he spent two years in postgraduate work abroad, chiefly in Berlin, Vienna and Prague. On his return to Cincinnati in 1893, he began general practice but continued his scientific work at the Cincinnati Hospital. While serving as curator of the laboratory he originated the first city-wide service for the bacteriological diagnosis of diphtheria, and with a group of colleagues gave the first course on clinical microscopy in Cincinnati.

In 1894 Dr. Bettmann was appointed pathologist to the Cincinnati Hospital. During the years that followed, he did much investigative work and published many papers, and in 1905 he won the Alvarenga prize for his monograph on "The Shape and Position of the Stomach." He served as pathologist until 1907, when a serious autopsy infection forced his resignation.

Early in his practice, Dr. Bettmann became interested in gastro-enterology. He was a charter member of the American Gastro-Enterological Society and was its President in 1920.

In 1921 he was appointed Director of the Medical Service of the Jewish Hospital of Cincinnati, and inaugurated the weekly clinical conferences at that institution, which he directed until his death.

In 1931 he was made Professor of Medicine in the University of Cincinnati College of Medicine, having held the rank of Associate Professor for a number of years previously. His course in gastroenterology was an outstanding one.

The claims of a large practice did not prevent his filling many other positions. He was President of the Academy of Medicine, Cincinnati, in 1927. He was one of the founders, and for many years a member of the governing body of the University School of Cincinnati. For over twenty-five years he was an active member of the board of the Public Library. He was intensely interested in belles léttres and had a profound knowledge of the masterpieces of English, French and German literature.

He was an amateur botanist of distinction; he was a world authority on chess problems. To his patients he was indeed the beloved physician. To his friends, his charm, his goodness and his loyalty were real sources of inspiration. He was an honor to his profession and his life work will endure. Of him it might well be said, " He loved truth and beauty and he never did an ignoble thing."

ALFRED FRIEDLANDER, M.D., F.A.C.P.

ERRATUM

" Chemical Studies in Myasthenia Gravis," by M. Adams, M. H. Power and W. M. Boothby. The sentence which begins in the last line of page 825 of the January issue should have read: If the five patients (cases 11, 3, 12, 13 and 14), who were all 65 years of age or more, and obese, are excluded from consideration, the coefficients of the remaining patients will be found to vary from 6.6 to 9.7.